

WEBVTT

NOTE duration:"01:11:27.0850000"

NOTE language:en-us

NOTE Confidence: 0.943438947200775

00:00:00.620 --> 00:00:08.850 Good morning. Everybody would like to get started with the Grand Round Season 2 night 2019, 2020 grand round season.

NOTE Confidence: 0.900607347488403

00:00:09.580 --> 00:00:22.090 It's fantastic to be here with all of you today great to get started and we have a wonderful grand rounds presentation in a bit and Joe Galanter will be introducing were not to our grand on speaker today.

NOTE Confidence: 0.12964640557766

00:00:22.970 --> 00:00:23.750 Uh.

NOTE Confidence: 0.880049049854279

00:00:24.980 --> 00:00:30.050 So let me I wanted to make a few comments.

NOTE Confidence: 0.945727407932281

00:00:30.620 --> 00:00:37.070 And I'm going to start out by getting the bad part of the announcements out of the way 1st and then go to the.

NOTE Confidence: 0.871240615844727

00:00:37.700 --> 00:00:40.750 To the exciting good happy parts.

NOTE Confidence: 0.920177102088928

00:00:41.420 --> 00:01:06.950 The bad parts of the announcement, the bad part of the announcement has to do with over the summer University report was issued that described in detail allegations made against a former professor in the Department of psychiatry Gene Redmond, who was found to have.

NOTE Confidence: 0.932284891605377

00:01:07.670 --> 00:01:16.510 Both coerced an sexually harassed undergraduates in his research station in Saint Kitts in the West Indies.

NOTE Confidence: 0.921474516391754

00:01:18.290 --> 00:01:38.350 Some of you may have read those articles. There were articles in the newspaper about it. Some of you may have read the report that report is available and we we meaning the executive committee of the Department will be sending out an email to people describing that event.

NOTE Confidence: 0.921950876712799

00:01:40.210 --> 00:01:52.350 And also providing links for support for people who feel are upset by the news or by the implications of that news.

NOTE Confidence: 0.933423101902008

00:01:55.160 --> 00:02:01.960 But it's a reminder about the vulnerability in any community.

NOTE Confidence: 0.960834860801697

00:02:02.540 --> 00:02:05.620 For sexual misconduct.

NOTE Confidence: 0.814321279525757

00:02:06.230 --> 00:02:09.770 And the tearable cost of that.

NOTE Confidence: 0.92354416847229

00:02:10.470 --> 00:02:21.100 Both for the victims and the perpetrator and you know, we do everything that we can in a community like ours to make sure that that sort of thing doesn't happen.

NOTE Confidence: 0.936860024929047

00:02:23.910 --> 00:02:30.080 But it it's obviously distressing to think that something like that can happen.

NOTE Confidence: 0.937892496585846

00:02:30.710 --> 00:02:34.860 Let's all work to make sure that it doesn't happen again.

NOTE Confidence: 0.908129572868347

00:02:39.650 --> 00:02:49.890 I'm not sure that there's anything more that I that I can say it's hard to move on to anything else after after sharing such distressing.

NOTE Confidence: 0.900886833667755

00:02:50.490 --> 00:02:54.840 News it's probably old news for some of you but.

NOTE Confidence: 0.551688015460968

00:02:55.550 --> 00:02:56.730 But.

NOTE Confidence: 0.942912399768829

00:02:57.300 --> 00:02:59.940 I think it was really it's really important.

NOTE Confidence: 0.954387068748474

00:03:00.570 --> 00:03:06.170 To acknowledge the reality of these kinds of things because if we don't talk about them.

NOTE Confidence: 0.909844875335693

00:03:06.810 --> 00:03:12.440 We can pretend like they don't happen and that is not a healthy thing for a community.

NOTE Confidence: 0.918368279933929

00:03:14.870 --> 00:03:35.710 So let me let me let me shift to the happiest of happy news, which is that it also this summer. We welcomed our new residency class to Yale. Their exceptional people were were thrilled to have them part of our community also our new class of psych interns and some new members of our faculty.

NOTE Confidence: 0.924997806549072

00:03:36.560 --> 00:03:48.850 And also part of the summer celebration celebration was the news of two new endowed professorships in the Department. These are 2 new.

NOTE Confidence: 0.910617530345917

00:03:49.430 --> 00:04:00.150 Recipients of the Elizabeth mirrors and how is Jamison professorships one of them is a professor Joy Hirsch and the other one? Is Stephanie O'Malley Professor Stephanie O'Malley?

NOTE Confidence: 0.916722118854523

00:04:01.140 --> 00:04:05.140 And that's really that's really just wonderful news as well.

NOTE Confidence: 0.942107617855072

00:04:08.310 --> 00:04:16.530 And I wanted to say 2 things about about grand rounds because I think that grand rounds are really an extremely important part of our community.

NOTE Confidence: 0.1318439245224

00:04:18.420 --> 00:04:19.180 Uh.

NOTE Confidence: 0.917847037315369

00:04:21.850 --> 00:04:33.540 The first is that that we've had the opportunity to consider setting up distributed video.

NOTE Confidence: 0.890391886234283

00:04:34.160 --> 00:04:36.350 Recording or whatever cortella.

NOTE Confidence: 0.935282230377197

00:04:36.980 --> 00:04:41.790 Presentation of grain round so that you could stay in your office all by yourself.

NOTE Confidence: 0.939411878585815

00:04:42.370 --> 00:04:45.570 And watch grand rounds on your computer?

NOTE Confidence: 0.902067959308624

00:04:46.080 --> 00:04:47.870 An interact with nobody.

NOTE Confidence: 0.663751244544983

00:04:49.420 --> 00:04:50.550 And.

NOTE Confidence: 0.908581554889679

00:04:51.460 --> 00:05:07.140 And I I'm going to suggest that the point of grand rounds that that that undermines the actual deep deep value of grand rounds in our community that the deep value of grand rounds is getting people together.

NOTE Confidence: 0.95856112241745

00:05:07.700 --> 00:05:09.250 All in the same room.

NOTE Confidence: 0.937496304512024

00:05:09.790 --> 00:05:33.150 Interacting getting to know everybody and importantly to interact with people who don't work in the same don't do the same kind of work that you do or don't have the same kind of background that you do who approached this kind of work from a completely different another perspective and to all come into the room and see how this mix.

NOTE Confidence: 0.900540351867676

00:05:33.720 --> 00:05:50.580 What comes out of the mix? What often comes out of the mix our friendships and find people that you like to interact with and people that you never met before you meet new people and and that's really valuable.

NOTE Confidence: 0.915014743804932

00:05:51.100 --> 00:06:00.280 And that that those connections that are made in grand rounds are really in some ways, the sub part of the substance of our Department.

NOTE Confidence: 0.949822902679443

00:06:00.880 --> 00:06:09.200 And I'd like to really encourage people to take advantage of this because the more people who come to grand rounds.

NOTE Confidence: 0.929550230503082

00:06:09.820 --> 00:06:39.190 The more valuable grand rounds becomes the more lively. The more exciting and the stronger our community as a whole becomes so I'd like you to really think about grand rounds as more than just the topic of the lecture of the day, but really the opportunity for us to get together as a community and work on getting to know each other and only good things come from that.

NOTE Confidence: 0.91777491569519

00:06:40.690 --> 00:06:45.690 The second thing about grand notices that I'm supposed to tell you about CME credits.

NOTE Confidence: 0.895016252994537

00:06:46.370 --> 00:07:00.060 And that is that if you want. See me credit. We know long for you know the faculty. We no longer have sign up sheets. You should have the site is psychiatry, GR at yale.edu and if you go to that site.

NOTE Confidence: 0.898338556289673

00:07:00.640 --> 00:07:06.690 You can get credit for your CME credit for grand rats and encourage you to do that.

NOTE Confidence: 0.345897674560547

00:07:07.200 --> 00:07:08.820 So.

NOTE Confidence: 0.168093785643578

00:07:09.430 --> 00:07:10.570 Uh.

NOTE Confidence: 0.818495094776154

00:07:12.280 --> 00:07:12.880 Oh yeah.

NOTE Confidence: 0.918160498142242

00:07:13.430 --> 00:07:18.960 I was going to tell you what's coming up, but that's on the other side of the page and I had to remember to turn over the page.

NOTE Confidence: 0.909792900085449

00:07:19.650 --> 00:07:50.540 So next week, we'll have a lecture by George Drugoi, who's a faculty member in our Department called Neural. Ensembles underlying internally generated representations in George does work on the part of the brain called Hippocampus and how the brain. The Hippocampus makes Maps of the spatial world around us, it's really innovative and exciting work.

NOTE Confidence: 0.916347622871399

00:07:50.540 --> 00:08:21.510 I commend that to you and then the following week, which is the 20th of September. Ariel Baskin Summers from the Department of psychology at Yale will be talking about understanding disinhibition from diagnosis to mechanism to treatment. She's in a very creative cognitive neuro scientist psychologist who studies impulsive behavior so see apathy things like that.

NOTE Confidence: 0.910801947116852

00:08:21.510 --> 00:08:23.790 And she's a really great speaker, she spoke at.

NOTE Confidence: 0.930812895298004

00:08:24.560 --> 00:08:26.850 The Community Neuroscience Conference last year.

NOTE Confidence: 0.90539014339447

00:08:27.590 --> 00:08:40.240 So those are the upcoming grand rounds lectures, which will follow the exceptional lecture that you're going to hear today and I'd like to invite doctor glendor up to the podium to introduce the speaker.

NOTE Confidence: 0.918992936611176

00:08:48.090 --> 00:08:52.520 So it's really a great pleasure for me to introduce Doctor Renado Paula Monte.

NOTE Confidence: 0.92501974105835

00:08:53.170 --> 00:09:03.330 He trained BS and Masters and PhD PhD in evolutionary biology at University of Rome Tor Vergata.

NOTE Confidence: 0.930860221385956

00:09:04.500 --> 00:09:08.590 He came to my group for a postdoc starting in 2013.

NOTE Confidence: 0.961152911186218

00:09:09.090 --> 00:09:13.010 He was created an assistant professor in our Department in 2017.

NOTE Confidence: 0.921297371387482

00:09:13.990 --> 00:09:22.670 He's done really exceptionally well across the board, he's done very well with grants with 2 NIHR 20 ones.

NOTE Confidence: 0.91545957326889

00:09:23.420 --> 00:09:26.450 5 private foundation grants, including and are sad.

NOTE Confidence: 0.926775336265564

00:09:27.040 --> 00:09:38.150 Multiple awards and honors, including the Simons Foundation Autism Research Initiative Explorer Award and a young investigator award.

NOTE Confidence: 0.9675013422966

00:09:38.790 --> 00:09:42.250 From the American Foundation for suicide prevention.

NOTE Confidence: 0.92443460226059

00:09:43.650 --> 00:10:02.990 He holds several editorial board positions and he's also Co editor with me in the Journal molecular neuropsychiatry. We're just taking over. We need to encourage submissions. If you have anything good send it to us. We want to raise the impact factor from imperceptible to something perceptible.

NOTE Confidence: 0.9435133934021

00:10:04.760 --> 00:10:24.230 He is already the author of 84 peer reviewed papers and about a half dozen more available on bio archive. Some of which are going

to be really, really big. He's published in excellent journals, biological psychiatry in molecular psychiatry in nature neuroscience.

NOTE Confidence: 0.915717422962189

00:10:25.750 --> 00:10:52.570 Renado is this sophisticated statistical geneticists. He's a key analyst both for the million veteran program and for the psychiatric genomics consortium. Sud substance use disorder group. He's made major contributions to numerous MVP papers. An is lead author on the new PGC opioid use disorder article, which is about to be submitted and he's not even going to have time to talk about that one today, but it's really good paper.

NOTE Confidence: 0.917540431022644

00:10:53.950 --> 00:11:07.430 He is really out sent outstanding young scientists and he's brought a lot to the psychiatric genetics research program that yell and he will bring a lot more so it's my pleasure to introduce Renado.

NOTE Confidence: 0.869951486587524

00:11:21.650 --> 00:11:50.440 Thank you for the introduction was really, really nice. Maybe too nice. So I'm going to talk about big data why we need big data in psychiatry genetics and so why we're using concerts are by banks city and signs to increase the sample size. And why we need this huge samples and if you want to take pictures. If so, if you want to do it. There is my address and so do it or don't do it is the same. I'm not that social so it's fine.

NOTE Confidence: 0.901929676532745

00:11:50.960 --> 00:12:12.240 So I have not conflict of interest. At least financial one. However, I have several academic interest. Human Genetics is my first is my love. Obviously biological psychiatry. I like really a lot evolutionary biology statistics. An computational biology. So I try to mix up these things because of the complexity of the.

NOTE Confidence: 0.893217921257019

00:12:13.150 --> 00:12:44.160 Issues that we have to investigate so my ultimate scientific goal is to link human genome and human freedom from different perspective and the reason is that the human genome is affected and shaped by multiple 40s. So on your right. We have 2 terms from publishing genetics. A human demographic history. Genetic tree for natural selection sexual selection. All these forces shape it. They genetically protector of human genome and they shipped also.

NOTE Confidence: 0.883268535137177

00:12:44.160 --> 00:13:15.190 David is position to main Dayton phenotypes and complex traits so in few slides I will explain the difference between a men. Darien trait and a complex trick, but 1st when you start to do some genetic research. Oh, this is the first thing that you notice and these are few figures from the human genome diversity project and the one thousand genome project. These

are not really reason, but the impact of these studies is outstanding in the in the human genetic field so on your right.

NOTE Confidence: 0.893270790576935

00:13:15.190 --> 00:13:45.800 You can see our fellow genetic tree of the human genome diversity project, which include 54 human population and you can see that there are clusters and each cluster is a continental group, so you have Africa Middle Eastern Europe. Central Asia is Stasia Amerindians and organic so we have this cluster and then from the human genome diversity project. We have a map of 24 population and yeah, we can see different pies and the dark.

NOTE Confidence: 0.897194981575012

00:13:45.800 --> 00:14:16.120 I am slicer agree doctor slices are the one that are variants that are present in multiple continental groups in multiple population and then we have the colored one there. The variants that are specific for a continental group offer a population. So we have some common variation and some ancestral specific variation and then here on the bottom. We have the number of variance in a human genome, so around 4 million, 4.2 million variance if you are not from.

NOTE Confidence: 0.897934257984161

00:14:16.120 --> 00:14:21.180 An African population in it, you can see here, the European E Asian Central Asian.

NOTE Confidence: 0.899840652942657

00:14:21.700 --> 00:14:48.190 I'm except that mix of American population are around the same amount 4 million variance and then you have the African population. So the threshold. Most 5,000,000 balancer and there is a reason for that. Humans are an African species. So there was an out of Africa, a bottleneck a reduction in the diversity so known African individuals are the outcome of these out of Africa. So there is this bottleneck and we have less value.

NOTE Confidence: 0.890024363994598

00:14:49.190 --> 00:15:20.100 So when we talk about variants and the main differences between a rare and common variance and again. The one thousand genomes data and here you can see the frequency the alterative frequencies. Because these example is a biallelic variance so one variant with two alleles are so you can see that much their highest number of variants are rare. More than ten millions variance and common variance are not that frequent so most of our genome is affected by a rare variance.

NOTE Confidence: 0.910143613815308

00:15:20.100 --> 00:15:45.700 And here you have the number of rare variants detected in the 24 one thousand genomes population and again. These are the African population and you have a higher number of rare variance in the

African genomes here. The color that one are the singletons balance that are detected, only in one individual so envios number is the same across all human populations.

NOTE Confidence: 0.88161563873291

00:15:46.580 --> 00:16:17.510 So coming back so we have the jeans. We have variants and what these things do they are linked to phenotypic expression. So we can distinguish between main dallion in multifactorial inheritance so in a million phenotype? Are you have a single gene a single mutation that is actually causing there's no type is 100% variance explain you can have modifiers jeans that are not causing definite type definite type is caused by a mutation the cows or notation.

NOTE Confidence: 0.899289548397064

00:16:17.510 --> 00:16:41.340 But I can change the Geno Type phenotype correlation so you're going to have individuals with the same notation and sometimes slightly different phenotypes and then we have the complex trait. We don't have a single causal variant. You have multiple sociative. Lee jeans and the next slide. I will show how many they are, and they combine a factor of these jeans token together with environmental risk factor.

NOTE Confidence: 0.870331823825836

00:16:42.030 --> 00:16:45.470 Lead to the onset of complex trades.

NOTE Confidence: 0.885526061058044

00:16:46.310 --> 00:17:00.980 So what about complex traitor, which will be the focus of my talk today as I said multiple genetic factors. We have also an environmental component. So we can, we can split this variance between.

NOTE Confidence: 0.872643291950226

00:17:01.480 --> 00:17:32.520 Did one due to the genetic component? They irritability and the one due to environmental component and one easy way to do it easy almost easy is twin studies, so determine the difference between identical twin and for technical after ternal twin. We can estimate the readability and we saw that across complex traits. There are traits with a higher readability and traits with a lower editability here, you have like different psychiatric disorders and you can go for.

NOTE Confidence: 0.894610702991486

00:17:32.520 --> 00:17:46.740 From 80%, almost 90% for bipolar schizophrenia to around 30% for generalized anxiety disorder, so all these second disorders have hub heritability. There is a genetic component.

NOTE Confidence: 0.889656662940979

00:17:47.820 --> 00:18:04.510 But what is the difference so let's Come Back to rare and common variance and yeah, I put an example. That is also the

spectrum disorder. I choose this example because I work on this thing and I was writing a grant popular few days ago, so I get this figure already but these results on Heather ISM.

NOTE Confidence: 0.893962502479553

00:18:05.190 --> 00:18:23.080 Like if you think about all this spectrum disorder. You think about red variance and they taught us a lot about the biology of this disorder here. You have a list of all jeans affected by rare variants. The novel, or inherited patterns and different syndromic forms and.

NOTE Confidence: 0.853812158107758

00:18:23.600 --> 00:18:30.130 If you go to an autizmus like when I go to the Simons Foundation meetings 80% of the Doc is about red vines.

NOTE Confidence: 0.896058619022369

00:18:30.670 --> 00:19:00.680 I don't work on invariants, they're nice but I like common, but it's better, so and if you see here. Common variance explained 49% of autism spectrum disorder, so rare variants are important. They are easy to understand because you have one gene affect the mechanism and you can create for example, are animal model and then from there threads on the stand by your job. This is common variants. They're much more complex, especially because the factor.

NOTE Confidence: 0.849259376525879

00:19:00.680 --> 00:19:05.420 It's really small and I will tell you how small it is so organicity.

NOTE Confidence: 0.88518750667572

00:19:06.270 --> 00:19:36.570 Here up another example schizophrenia and is the lifetime risk of schizophrenia, depending on the relationship with an effect that patient so you have a monozygotic twin and you share 100% of the of your genome with these models regarding twin and your risk are to develop schizophrenia is 48%. But then you can have like a basically to insert children. Sibling parents and you share 50% of the genome and your risk goes from.

NOTE Confidence: 0.87786477804184

00:19:36.570 --> 00:20:07.860 17 to 6% and then maybe you are a second degree relative and your is go from 6 to 2%. Or maybe you are a 30 degree laurate if you risk is 2% or you are are related to their patient. So, your degenerate disc in the population is 1%. This means that we don't have probably up schizophrenia gene but there are multiple jeans. How many we don't know we have estimates. I will show how many they could be so if you have multiple jeans.

NOTE Confidence: 0.876016795635223

00:20:07.860 --> 00:20:31.070 This is the risk a stratified if you have one variant so we have a higher risk. If you have 2 copies of the variant. If you have 2

council jeans for copies is the highest grouper or people with risk. Chris nips 10 snips 100 increases the number you start to have Bell shaped curve and you will have on the Taylor.

NOTE Confidence: 0.630427420139313

00:20:33.330 --> 00:20:33.690 Sorry.

NOTE Confidence: 0.852007269859314

00:20:34.480 --> 00:20:49.040 Yeah, we have on the table people with high risk they cover a lot of risk variance. So we know that common tree. Common variants are associated with your disorder, they explain a lot of definitely pick variance.

NOTE Confidence: 0.89572662115097

00:20:49.930 --> 00:21:20.030 They are many variants we have to find a balance so there are different approaches and they were developed depending of the technology that was available at the time so initially we had family linkage study. They were contacted on informative families so finish that have multiple cases and then at the time we were able to investigate informative marker across the genome. There wasn't really dancer so we had few informative variant. I thought informative markets and from that.

NOTE Confidence: 0.8798508644104

00:21:20.030 --> 00:21:42.740 We're going to defy shared region across these family members and from that arrived to the Mutation and from the position. We can have an iPod. This is this kind of approach work really well. If you have a large effect size. I will talk later there about large effect size but doesn't work that well for common variance so another approach is maybe you have on a policy about what is?

NOTE Confidence: 0.868521749973297

00:21:43.300 --> 00:22:10.010 The cause of your disease and among disable. This is you find the Jeep that you really like and this is this is the general is doing that is causing this phenotype and we did that gene you have one variant and is developed that maybe is a city with a protein change and you think, OK did say I'm going to do my candidate Agenus Fission Studies comparing cases and controls and I want to see if the cases have higher frequencies of these deleterious variants.

NOTE Confidence: 0.901263058185577

00:22:10.840 --> 00:22:19.980 Unfortunately didn't work that well because there is a problem. We are really bad to make any policies and I will explain in the next slide? Why we're really that, but there are few example if you exception.

NOTE Confidence: 0.865721166133881

00:22:20.600 --> 00:22:51.130 So then we have genome wide Association studies. These are hypothesis free. We don't have any policies. We test the entire genome when it large sample size. I will talk later about our larger, we find a sniper's knippa then common button to Gina from that animal is so let's talk briefly about converging studies. Everyone's is Feb Bridge in high have might have a gene is the one that I started like almost 10 years ago, when I was doing my master places, but we now know that.

NOTE Confidence: 0.883044838905334

00:22:51.130 --> 00:23:21.390 Most of this country jeans, they are not really relevant for different type and these 2 papers, they analyze schizophrenia convey jeans and depression. Canada jeans and they found in most of the cases there is no support. There is no evidence that they were real signal on further is still a lot of people are doing 100. Gina solution studies and you shouldn't do it. However, we have few exceptions, like for example, a plea in Alzheimer's Research or alchemy.

NOTE Confidence: 0.841671884059906

00:23:21.390 --> 00:23:36.950 How old is Jim in our code research these were detected in College in Association studies and their replicated in G wars because if the violent is really important. You should find it also in a divorce study so before to start planning approach.

NOTE Confidence: 0.853530406951904

00:23:37.460 --> 00:23:38.650 Take a look at today?

NOTE Confidence: 0.888451099395752

00:23:39.300 --> 00:24:05.550 Files country jeans, a hypothesis that we did in the past. We are, we have to learn from that because these issues caused a replication crisis in Human Genetics, so because when we were starting to do Association studies. We were saying OK. We got the gene. This is it and then one was able to replicate it because the simple size was too small and the gene was not really level. So we move from there when the technology parameters to investigate.

NOTE Confidence: 0.932097673416138

00:24:06.100 --> 00:24:10.290 Thousands hundreds of thousands and now millions of variance across the genome.

NOTE Confidence: 0.871250569820404

00:24:10.870 --> 00:24:41.390 To do a genome wide Association studies genome wider social studies. G was are not elegant experiments. This a brute force experiment. I am testing everything because I have no idea what's going on so we use arrays that can genotype millions of violence and then impute other variants so virus that we did in Geno type. But through a reference panel

from sequencing data. We can predict other variance drew due to their linkages equilibrium.

NOTE Confidence: 0.893988490104675

00:24:41.390 --> 00:25:03.680 They correlation that we have among these variants so right now, you can have a Jewelers plus in position that arrive to more than 10,000,000 variants 50,000,000 variants so this is a lot of information and there is a lot of way. You can screw things up so you have to be really careful because it's a lot of power. When you use this brute Forks, brute force experiments. You have to be really careful and you have to know what you are doing so.

NOTE Confidence: 0.904695093631744

00:25:04.390 --> 00:25:12.050 What kind of violence we can detect without you was there is a relationship between a Lil frequency and the effect size.

NOTE Confidence: 0.883736610412598

00:25:12.570 --> 00:25:19.110 How much risk is associated with that variant so when you have a mendel and disorder you are here?

NOTE Confidence: 0.853190720081329

00:25:19.720 --> 00:25:49.930 The variant is really rare they fat is huge in some cases, if these are Mendel and trade explain completely different typic clients and then you can have you exception as I said a buoy the CFH variant is to say that with the age macular degeneration and the other variants and these are exceptions. So when we did the first was we found this balance, only because we're conducting a small studies and then from that, increasing the sample size. We started to find.

NOTE Confidence: 0.884853839874268

00:25:49.930 --> 00:25:54.020 A lot of variance they were common here with tiny effect size.

NOTE Confidence: 0.861696898937225

00:25:54.750 --> 00:25:58.370 So this what means that first.

NOTE Confidence: 0.895668745040894

00:25:59.070 --> 00:26:29.400 Complex street are highly polygenic, then we need huge sample size. Big data to cracker. The genetics of these complex 3 and each complex trait is different. They don't work in the same way so in this life. We have 4 trade. Inflammatory bowel disease height, schizophrenia and bipolar disorder. So you can see that for IBD when they started with you was an Abd there were super happy because they were doing like a Jules with 5000 subjects and then with 5000 subjects.

NOTE Confidence: 0.884751915931702

00:26:29.400 --> 00:27:00.430 They got 100 Gina White significant those are generated significant low side is variant are variance that survive a multiple testing correction for in Tachira. So they were Super Laggy. We need it. We got it. That's good, but for other traits that didn't work that well for example, for it. It was working fine here. When we started. We didn't know how large should be this sample, so 5000 look like. These are big number. We now know that 5000 is a tiny number so for item. We started to do like 10,000 cases.

NOTE Confidence: 0.899046182632446

00:27:00.430 --> 00:27:30.640 And we got a lot of variance and then increasing it went better for a second disorder. We were not that lucky because 2nd result. Then it's much higher sample size. You can see here. The dead zone. That's done when you have add samples so you don't find anything. It's pretty bad for schizophrenia. Bipolar disorder and then it comes up when you reach a certain point, and that point is the inflection point that you reach when you start to have the power to that the tiny effect sizes.

NOTE Confidence: 0.870758414268494

00:27:30.640 --> 00:27:40.510 Data set with that train at we predicted a certain point, we should reach a plateau where increasing the sample size. We will not detect anything we found everything that we need.

NOTE Confidence: 0.894154250621796

00:27:41.360 --> 00:28:09.840 So this is the reason why we need large sample size N where we get can get these samples. One approaches to bring data together so in Secondly genetics at certain point. They start to think we're not finding anything by Ourselves. We have to bring the data together and create our concerts and so this thing I think started more than 10 years ago and will start to buy Patrick Sullivan from you and see. And when we started to make this.

NOTE Confidence: 0.889201521873474

00:28:10.560 --> 00:28:40.810 Talks about we have to come together bring data together analyze data in the same way. People were not really happy about that was at the end, he was able to found the cigarette Genomic concert so right now. We are more than 1000 investigators across them. The world and is the largest concert some in the in the second item and AMC story well fundamental biology improve. A clinical practice and find provided targets so we are in the 3rd funding iteration of PC and the goal.

NOTE Confidence: 0.90921151638031

00:28:40.810 --> 00:28:48.970 Storage 100,000 cases there were group and right now, we have, we achieved that goal for depression and schizophrenia.

NOTE Confidence: 0.874903857707977

00:28:49.590 --> 00:29:20.000 And we're not there for the other because we have different work group are ADHD autism bipolar depression. And there is

substance use disorder group, so we're not that yet, but we have also other concerts in enforce a geyser here is a list of different concerts. And there are other relevant for surviving for example, the anxiety narrow genetic study. The Enigma, studying about brain imaging. There is the Social Science Genetic Association consortium and the tobacco and genetic concerts and there are other concerts are for other traits.

NOTE Confidence: 0.880252301692963

00:29:20.150 --> 00:29:28.560 So this is one approach, you have studies. They were collected are recruited for a specific a cluster of disease and you bring the data together.

NOTE Confidence: 0.895505964756012

00:29:29.810 --> 00:29:57.880 Another approach is bio bank so I'm talking about National Bank and they are the largest one and the first one, is the UK biobank and is not the first but is the one they made the largest impact on human genetic research and in numerous search in general because first of all there are good at 500,000 people. Middle age more than 4000 phenotype assessable brain imaging phenotype. They are going to release so body image in final diaper.

NOTE Confidence: 0.821516692638397

00:29:58.610 --> 00:29:59.300 But they

NOTE Confidence: 0.910613477230072

00:30:00.040 --> 00:30:24.050 Nicest thing that they did. They opened by bank to everyone right now any scientists around the world can apply to get the data pay a small fee around \$5000. Maybe less if you don't need like all the data and you can get the data. You can do your own analysis. So, there are I think right now. Thousands of scientists working on this data, and a lot of papers coming out so these.

NOTE Confidence: 0.885607063770294

00:30:24.810 --> 00:30:27.710 Data source generate the eye huge amount of information.

NOTE Confidence: 0.887034237384796

00:30:28.740 --> 00:30:39.450 So another bank for example, is the million veteran program right now, we have more than 750,000 veterans are recruited is.

NOTE Confidence: 0.873538255691528

00:30:40.980 --> 00:30:44.440 Is is across the US? We have different centers?

NOTE Confidence: 0.840120792388916

00:30:45.140 --> 00:31:15.150 And focus on multiple projects and the four flood project that you can see on the website that about a period. PST cancer risk and cardiovascular diseases and jeweler together. Other peas in the VA are

living body. Opioid enter PTSD analysis. So, how is different they MVP from the OK back MVP is not open to everyone to access MVP data you have to be up. VA investigator, and then you, you need to get fun that.

NOTE Confidence: 0.900894105434418

00:31:15.150 --> 00:31:31.550 Time between mechanism and then you can get access, so the accessor is still limited and these are working in progress. So it is making an impact, but it is not faster like the UK back because there are not that many investigator working right now on this data.

NOTE Confidence: 0.91111832857132

00:31:32.370 --> 00:32:04.240 And then we have the US version of the UK biobank. They all of us a a research program. The goal is to recruit more than one million individuals across the US and right now there is a website. You can go with a browser and you can check the data. They have information about more than 100,000 individuals and is going to make a huge impact because the difference between these by your back and the UK biobank is that this by bank reflects the genetic diversity of the US population.

NOTE Confidence: 0.882722675800323

00:32:04.240 --> 00:32:16.790 Like the you back cable banker is around 95%, you will be under sent this by your back is much more diverse. So it's going to contribute more to understand differences across ethnic groups.

NOTE Confidence: 0.887601673603058

00:32:17.990 --> 00:32:39.020 And then we have also other kind of bio bags much smaller like institution biobanks. For example, Vanderbyl Harbor and there is also in processor at the Yale Biobank with the goal to recruit more than 100,000 subjects and wall. Exome sequencing on the subject and bring the data to to the clinical practice.

NOTE Confidence: 0.879273056983948

00:32:40.380 --> 00:33:11.680 So what does Syrians in science and this is another way that scientists are getting data so right now there are companies and you can send them your saliva and I will give you some information. The most known is 23 and me, I did here is my stuff and it's surprising them Italian as you can hear from my Dick accent, but I have also 7% of Middle Eastern a answer that I didn't know and I can provide all this information about how old was your connection.

NOTE Confidence: 0.878695964813232

00:33:11.680 --> 00:33:36.840 With that with these other ancestor group, so other companies can provide similar evidence about like answer.com, but I thinks about 20 from me. And they did this from the start is that they want to

provide healthcare information. So you're going to information about predisposition like you're a bully. Genotype are other balance with large effect carrier status for a lot of a variance.

NOTE Confidence: 0.902618527412415

00:33:37.430 --> 00:34:08.260 That can be associated with a rare and medallion trades so you have a lot of information if you heard about the solid winter me. They started with the elkarra information and then when stopped by the FDA and a couple of years again and they got back with information and there's a big discussion of our reliable are these data because for example, in some cases, there're story about people that got positive results for rare variant with a large effect and then they went to a clinical laboratory.

NOTE Confidence: 0.887845754623413

00:34:08.260 --> 00:34:38.340 And the Journal I was not confirmed so there are some issues about our reliable. All this data that right now. There are more than 10,000,000 customer for 20 to me and is a huge amount of data that scientists are using because you can feel a question. It online and people can use this data, you can say OK. I want to participate to research and your data will be shared with the 20 me collaborator so most like academics looper and pharmaceutical companies so there is also up.

NOTE Confidence: 0.888862073421478

00:34:38.900 --> 00:35:09.080 Some points to this customer and this is not there. The place so what's the difference, about consortia biobanks and genetic testing company so the first in a concerts are usually samples are recorded with a specific pros are group of this is our specific disease. So usually you have a deep phenotypic characterization. But the opposite is they were collected by different groups. So, sometimes, they use different instruments. So there is a Trojan in the assessment so it takes a lot of time to harmonize.

NOTE Confidence: 0.874263763427734

00:35:09.080 --> 00:35:37.530 This panel type and then you have the bank. You have a large sample like when is our National Bank UK biobank MVP all over some but is representative of the general population so when you have a rear over uncommon disorders. Your these sample. It can be larger like 1,000,000 subjects, but still you will have a low prevalence of these disorders, so we will talk power to detect to investigate this kind of disease.

NOTE Confidence: 0.876990258693695

00:35:38.110 --> 00:36:08.180 And then we have a student sign genetic testing massive sample size, but they if in typical edition is really alone because mostly is our online question are so it's not really deep like when they did. The first depression. She was on 23andMe data. They were 3 questions and you work at because there's a process was huge, but still there is a big question there are

a couple of papers one from General Flynn. I can cancel about our definitive icator genetix is affecting.

NOTE Confidence: 0.842835962772369

00:36:08.180 --> 00:36:11.560 The op genetic results and there is an ongoing discussion so.

NOTE Confidence: 0.867161095142365

00:36:12.530 --> 00:36:19.490 Let's talk about second is order and she was and out. The simple size can impact your result.

NOTE Confidence: 0.850850462913513

00:36:20.180 --> 00:36:36.840 So here are 2G was from PC is a galley Genomic and sort of lesson 11 about 10,000 cases. 12,000 control, so they found 5 Jenna whites, giving a lot also balance that survived the bonferroni correction accounting for the entire genome.

NOTE Confidence: 0.895331025123596

00:36:37.390 --> 00:37:07.470 And then like 3 years later, 37,000 cases more than 100,000 controls they got more than 100 gigawatts, keeping a low so this is only power. These are brute force experiment, they found a lot of jeans and there was a huge impact. I remember there was this. It was 2014 was my first SOBP meeting and they the SVP is not a meeting focus on second genetics. But I saw these monotone plot, many times because there were people investigating each of these variants.

NOTE Confidence: 0.870451033115387

00:37:07.470 --> 00:37:38.220 And now they were affecting schizophrenia disorder, so how to read the American plot here. You have chromosomes so you have 22 or plus a day sexual chromosomes and here you have the negative log. 10 P value so higher is your peak strongest is the Association each dot is a variant so sometimes you have a column and this is due to the linkages with the correlation among the variance. So when I'm saying 100 University. Marlow say I'm seeing 100 independence signal across the genome.

NOTE Confidence: 0.900218605995178

00:37:38.880 --> 00:37:47.650 And this is the factor for major depression. So 2013, 10,000 cases that as a control nodding and then.

NOTE Confidence: 0.908360660076141

00:37:48.190 --> 00:38:18.430 This year I huge amount of data 250,000 cases more than 500,000 controls they found 100 and why is it 102 generalizing loci if you compare these 2 traits depression and schizophrenia. You can notice a difference like with a much larger sample size. They got the same amount of Jenna. White ceiling low side, so this means. Maybe that depression is more full check so I'll talk about this later so there was a time back in 2012.

NOTE Confidence: 0.878785967826843

00:38:18.430 --> 00:38:48.790 Before we reach these large sample size that found engages in was almost a funding issue where almost shutting down PC because as I said, we had zone. There was really deeper for a second disorder, so they were saying, You was a is not the right approach for for for psychiatry. So there was the letter from Paris. Alvin and the other 96 P eyes in PC don't give up on us. And they were right because we were closed. We needed only more samples and Why is that?

NOTE Confidence: 0.891287565231323

00:38:48.790 --> 00:39:11.950 This is, do as I said to the fact that we have small effect size. Yes, you can see here. So here are 2 density plot for continuous trait and disease here. You have the effect size here, you have the density and you can see here that you have 2 pixel. One is from neuroticism and you have this means that effects eyes are really tiny.

NOTE Confidence: 0.877552688121796

00:39:12.800 --> 00:39:43.000 Here, most of the variants are in this place and the other one here is depression. The one in the light blue dotted line. This means and explain why we get this effect? Why we need a much larger sample to get 100 Watts in a Las because the fact size are much smaller, so there are different type of this is to explain this effect. One is data ability like depression is a much more literal general so phenotype than schizophrenia so.

NOTE Confidence: 0.877414762973785

00:39:43.000 --> 00:39:57.090 We may have multiple soup phenotypes and with different genetic architecture and the other is that evolutionary pressure like I say there are multiple aspects that interact together so profound selection is a mechanism by which.

NOTE Confidence: 0.885626673698425

00:39:58.390 --> 00:40:28.610 Select the pressure remove variance with a deleterious effect from the population. So there are certain genes in particular, brain genes. There are strong evolutionary pressure. This means that balance would larger fact are removed. So they have a really low frequency in the human population, so this effect is particularly may be particularly strong in depression, but is present across also Garrity's order. So here is a different kind of Melotone Plotter, you have chromosomes here.

NOTE Confidence: 0.860461235046387

00:40:28.610 --> 00:41:00.080 Here you don't have P values here have varied ability and so higher is the big them or eligibly. You have in that specific region and we have here 3 traits dyslipidemia hypertension and schizophrenia. And here you can see we have high really high. Pickers they explain that up to 1% of their phenotypic variance for example, Chromosome 19. What is the haploid gene

but you don't have any high pic for schizophrenia and then in this study they did like a simulation analysis.

NOTE Confidence: 0.891434490680695

00:41:00.080 --> 00:41:13.600 This is the percentage of the genome where you about 0 Editability estimate and is really low for a schizophrenia and to explain these low portion of the genome without any kind of readability.

NOTE Confidence: 0.885886669158936

00:41:14.210 --> 00:41:37.190 For a schizophrenia, you need 20,000 variants. This means you have 20,000 cows are balance with tiny effect for schizophrenia. About 10,000 gallons for aggravation at 2000 variance for dyslipidemia so this means that when you do what you also for these 2 traits. You need a much smaller sample size to get these variants. Instead, with 25,000 with Tonya Effects. You need a much larger sample size.

NOTE Confidence: 0.86743575334549

00:41:38.150 --> 00:42:09.420 So poor genic that's it now, we won't think saving more complex that that so apologetic or only genic like a couple of years ago, he came out of from Jonathan preacher at Stanford and he came out with this idea. Maybe it's not polygenic. Maybe is only genic only. Jenny means that is not 20,000 variants is the entire genome that is affecting David disposition to complex trait and we came out with this data that was publishing in sell this year about the relationship.

NOTE Confidence: 0.876718759536743

00:42:09.420 --> 00:42:40.530 Of a gene expression so use gene expression data to explain these policies in the body disease that you have some core jeans. There are directly affecting definitely different type that you are interested and then you have all the peripheral jeans. They are link to the core jeans and they are affecting the core jeans and they will also be assertive with the offer a type that is in Direct Association. So apologetic only genic that's really complex. A and the jewels are helping us and now we have, Like A.

NOTE Confidence: 0.887987434864044

00:42:40.530 --> 00:43:07.240 Thousands of Genetic Association. These are a plot and that is really well known in genetics from the Jewelers catalog of where there are the list of all the gene's imbalance identified you have that 22 chromosome or plus the two sex chromosomes and each dot is a genetic Association. Each color is a different domain. And here you can see that is everywhere is highly polygenic so RG was greater.

NOTE Confidence: 0.87391722202301

00:43:08.080 --> 00:43:38.770 Depending on the day so missing eligibility is the big issue for Gibbosa Beauses. The mismatch between the twin study and that you was results so I show you before that, we force again with this order. We

have, like from 80 to 30% of variance explained by genetic factors and then we have 2 cases of missing a readability. The 1st is the old case so you do your schizophrenic G words schizophrenia as a highly percent 80% editability.

NOTE Confidence: 0.890902996063232

00:43:38.770 --> 00:43:55.300 And then you get only 5 variants from that, and you say? Where is the readability I should have much more a larger number of but it's at least this 5 should explain higher balance in still explain very, very little so the first case is explained by we are not really powered.

NOTE Confidence: 0.878753006458282

00:43:55.920 --> 00:44:10.070 We were not really power to the violence in the tiny effects. But we have also recent case so we have these huge amount of data hundreds of variants, but still dated ability estimates that we have from the jewels is much lower.

NOTE Confidence: 0.862734913825989

00:44:10.740 --> 00:44:21.200 From the one they website from twin style, so schizophrenia, 80% from twin study. She was of schizophrenia, 20 percent 25%, so we are missing a big chunk.

NOTE Confidence: 0.882230818271637

00:44:22.170 --> 00:44:53.040 But these today this year come it came out paper home by archive. I still a printer. So they found the missing readability as I said when you have a good you was plus invitation. You can reach up to 20,000,000 variance and these are editability estimates. I'm not going into details here for height and BMI. And here you can see with high do you have another ability between around 60% for BMI between 25 and 30%?

NOTE Confidence: 0.890491604804993

00:44:53.040 --> 00:45:24.110 And then with the wall genome sequencing, so you are sequencing, the subjects. You don't find only the balance that you have the props to but you find all the variants you reach are much higher number of balance 47 million variants and they found they calculated it ability and they found an increased so for item between 75 and 80% for BMI. I'm reading 40% and so there is a chunk of variance that we are not able to investigate with the standard G was approach.

NOTE Confidence: 0.838240742683411

00:45:24.180 --> 00:45:39.150 And at the violent with low LD here balance that are not correlated with other variance that we cannot impute and they're bringing emissary ability, so this work, it for height and BMI and this straight work it really.

NOTE Confidence: 0.895139276981354

00:45:40.160 --> 00:45:47.230 Fine with you was we don't know if these things is going to work for psychiatric disorders or other complex trait.

NOTE Confidence: 0.895870387554169

00:45:48.140 --> 00:46:19.090 So why you are not doing your genome sequencing if they are better than you was because were genome sequencing are much more expensive than she was right now to the jewels in one subject. You spend around \$100 for doing a virginal sequencing in an individual is about \$1000 so since you still need. The huge separate size because the effect size are still really small. We don't have right now. They possibly going to Wergin on sequencing on a huge sample size, so it's coming.

NOTE Confidence: 0.847985029220581

00:46:19.090 --> 00:46:24.380 Let's up the price will go down or like concert. Some people bring war genome sequencing data together.

NOTE Confidence: 0.875524342060089

00:46:24.920 --> 00:46:44.210 So what we can do in the mean time with the divorce data. One approach is polygenic. Lee score so here we have our Manhattan plot and and this was a really good. You was because we have a lot of buttons that Survivor Deline. The Jenna Wise significant threshold so we have these small effect size.

NOTE Confidence: 0.880246996879578

00:46:44.900 --> 00:47:16.910 A list of variance so we can create a score that some the effect of each variant and the number of risk balance that you have in each individual and so you can calculate a score for each subjects in your court and and there is a really nice article. In biological society about our review article about Pijper General scorer in a psychiatric disorders, so that there are different methods that you can collect Poly generally score. So the this summer, is the easy example and there are different to show that you can consider.

NOTE Confidence: 0.898558497428894

00:47:16.910 --> 00:47:47.010 So at the end, you will have a number that you can put near your subjects and what you can do with death. So there is a big ongoing discussion about OK. We have these virginity score. We can stratify our population for genetic risk and maybe we can tell table with the higher risk, you have a hyper disposition to develop these disorders and some other people say no poor generally score works. But in research. You have a lot of issues like population stratification differences across and play other bills so.

NOTE Confidence: 0.864567399024963

00:47:47.060 --> 00:48:09.220 Cause sometimes your originary score is not predicting your trait is predicting something else, so in last year came out. This paper or measured genetics and yeah, you have your distribution that you have

your fortune is core in your court and I did it for different complex trades no cigarette disorder Unfortunately and.

NOTE Confidence: 0.887630224227905

00:48:09.830 --> 00:48:40.580 They found that if you stratify your sample for the highest person tell people with a high risk genetic risk, you can have like threefold fourfold 5 four to impress a risk depending on their shoulder. You considering this is the example for coronary artery disease. You have the difference between control and cases and then you if you plot the percentile of your polygenic risk or distribution and the prevalence of the disease. You see that people with the highest in the highest percentile of a much higher.

NOTE Confidence: 0.882833659648895

00:48:40.580 --> 00:48:47.970 Prevalence of the disorder so there is a big ongoing discussion about should be moved polygonally score.

NOTE Confidence: 0.87355625629425

00:48:48.890 --> 00:49:12.440 To clinical practice, especially because in some cases, they projected score is predicting the same risk that you are now using for monogenic a mutation so there are monetary quotation aside with like lipid levels. There right now. You are telling people you have this mutation you have this familiarity. You should change your habits, but we can have something similar with for the general score.

NOTE Confidence: 0.884189188480377

00:49:13.090 --> 00:49:43.950 So the problem is that for margin. Mutation is much easier because there is only one way to calculate you have the variance. You don't have the balance for polygenic score. There are thousands of way to look. This data compare the lowest person tile to the Top percentiles. So it is really complex, but people can right now access for general score. This again my own data from twenty me and they provide originally school information about Type 2 diabetes, so in the US.

NOTE Confidence: 0.915549993515015

00:49:43.950 --> 00:50:01.500 Right now there are 10,000,000 people that can access this information and they probably they have a white paper on the website is not for reviewed and if you see here. The predictive power of across different answer is not that good and also the way they explain.

NOTE Confidence: 0.773868381977081

00:50:02.280 --> 00:50:05.880 The project is Cora your risk is not that.

NOTE Confidence: 0.902533531188965

00:50:06.500 --> 00:50:36.510 Careful they basically they're saying that you are in the typical range. I have personally out 20% chance of developing type 2 diabetes between my age and they are sold they can they can provide the risk

across different age group. But what this means so we could have like people like I work in genetic so I know that this is not really reliable and doesn't mean really anything right now, but you can have people going to their clinician and saying OK. I didn't want to.

NOTE Confidence: 0.848808169364929

00:50:36.510 --> 00:50:39.250 Me and they're saying that I'm going to develop diabetes.

NOTE Confidence: 0.883596777915955

00:50:40.110 --> 00:50:59.260 And the ignition should know maybe those genetics, so explain how this is nothing really has no idea what genetic keys and specially because polygonally score is really an area that is not where known for example, in clinical genetics, where they focus on Mutation. So it depends on what kind of background each clinician is.

NOTE Confidence: 0.503070771694183

00:51:00.040 --> 00:51:00.590 So.

NOTE Confidence: 0.911684215068817

00:51:01.350 --> 00:51:31.520 People have access, but there is also another project, the emerger electronic medical records genomics. We are in the 4th iteration the previous one. They mostly foreground variants. We large effect out to get back to the patients and integrate. Genomic information with the health with electronic health records. And in the 4th iteration that is under construction right now that should start in 2020 to 2025 they want to assess.

NOTE Confidence: 0.83323460817337

00:51:31.520 --> 00:51:41.350 The Genomic risk and now you can use the Genomic risk to manage patching patients and to change your elkarra possibility.

NOTE Confidence: 0.876052021980286

00:51:41.870 --> 00:52:12.120 So if you see here, you have different center. They were involved in the merger and if you look carefully. There is not Yale. That's a shame so we're going to change that. We're trying to so we put together a proposal. There is Geordies me. There is John Crystal and many other industries are both from psychiatry and promoted departments and we want to try to do is jeremic risk assessment in the year left, Kira system So what about psychiatry in our image proposal. We have a lot of 2nd disorders.

NOTE Confidence: 0.881658792495728

00:52:12.120 --> 00:52:43.010 But there is also psyche merger that is led by Jordan smaller anelia. Davis and they're trying to put together data from different by banks additional bio bank so there is Vanderbilt preserver them and put it around a Jelly information with the electronic health records. And this is the schizophrenia. Paul general score, which is the most powerful right

now in in psychiatry and you can see here. The predictive power of schizophrenia with respect to schizophrenia in their electronic health record.

NOTE Confidence: 0.85774439573288

00:52:43.010 --> 00:53:13.080 Another desert that same phenotype so, so you have psychosis. You have other scheduling are disorders. You have PTSD bipolar so side behaviors and so on. But here you can see, there are two ways to the took the data. The first the blue one. You can you compare the Top decile with the bottom the size of the score and you can see the fact is margil is much larger and then you have the Top decile this. I love this is the score versus the remaining distribution so.

NOTE Confidence: 0.90435802936554

00:53:13.120 --> 00:53:43.190 Which one are you going to use? Which one is the right one that's a big problem. But if you want to bring the information back if you want to stratify the population. According to this course, so this is a big issue and probably with the emails are we will be able to fix that, or at least trying to in the mean time in my group who we really love for general score. And we work. Also on autism spectrum disorder, so and we are accused because I save them a lot of the variance.

NOTE Confidence: 0.857282280921936

00:53:43.190 --> 00:54:14.130 In audio is explained by common variance, but a lot of people that don't have the disease. They have risk alleles for for these disorders, so we did an analysis and this is Frank Post, Doc in my group and we did the analysis using the PC. This ideology number concert. Some audios knew was there is not that larger, but is the variance explained but it was is desired, and you expect for other traits and we use the Philadelphia never drive Concorde investigated more than 500.

NOTE Confidence: 0.912414729595184

00:54:14.130 --> 00:54:19.410 Types of assessing in these children and we found out that in this particular middle.

NOTE Confidence: 0.8847616314888

00:54:20.260 --> 00:54:30.600 Age group are significant result for the Association between the audience mopol generate score and the ability to recognize angry faces and.

NOTE Confidence: 0.893801987171173

00:54:31.620 --> 00:54:45.310 This was significant in the Middle Group and replicated in the other group and here we can do the same thing we can stratify the risk across the population that we tested and we can see that people would.

NOTE Confidence: 0.881445527076721

00:54:45.820 --> 00:55:16.520 That carry more audience risk real they were much higher increase in this case not risk, but ability to recognize angry faces if you this is a complex story and we have different about this is so if you want to read the full thing. There is a prep Inter on Meadow Drive and you can read the whole analysis, but there are other things that we are interested and other things is the genetic correlation. So we have this player. Tropic mechanism when one balance is asserted with multiple trades.

NOTE Confidence: 0.877855777740479

00:55:16.520 --> 00:55:46.930 So this figure is from the brainstorm course or some other consortium. There is a court source am up concerts because they bring together brought together orgy was from different brain rather disorder. So 25 brain disorder 17 from types. More than one million individuals a was a huge analysis and they found genetic correlation. But what genetic correlation means genetic correlation means that you have a balance as I said that is associated with multiple phenotypes, but this could be due to different mechanisms.

NOTE Confidence: 0.852541387081146

00:55:46.930 --> 00:56:18.450 One mechanism is the vertical play Ottery when you have your variant. These associated with the 1st. No type and then he said. With the second flow type, so if you test the genetic correlation between these 2 you find there is a genetic overlap, but is actually due to the causal effect of P1 on people and then you can have an origin taklya to be where the variant. G is a sort of with the two phenotypes in dependently. This means that are independent mechanism. There is not causal Association with the P1 MP 2.

NOTE Confidence: 0.909592628479004

00:56:18.450 --> 00:56:24.720 So a big problem in Epidemiology is to distinguish between Association and causal effect.

NOTE Confidence: 0.905723750591278

00:56:25.470 --> 00:56:56.340 And the best way to do it is to do a randomized, controlled trial and test the causal effect between phenotypes. But we can use genetic information to do a similar experiment, so a Mandela randomization study when you use genetic information to stratify our sample between people with high risk for example of low LDL cholesterol and the other people have for example, looking for cardiovascular events. This is the is the example and you can find that using genetic information is useful be cause.

NOTE Confidence: 0.895047307014465

00:56:56.340 --> 00:57:26.730 Genetic information are not biased by environmental factor. So, your cholesterol level is biased by your diet your physical activity and other environmental factor your genetic disposition to develop a certain level of LDL cholesterol is not linking by the environmental factors so changing your diet is not going to change your jeans. You can change your

level, so using these jedec instrument. You can remove the confirmed in factor of several environmental.

NOTE Confidence: 0.89952552318573

00:57:26.730 --> 00:57:57.940 Risk factors so we did these analysis that a letter from the psychiatric genomics consortium. We tested the Association between post dramatic stress disorder and educational attainment and we use different approach different instruments are little different disorder and what we found is that there is a negative Association between PST and educational attainment in this direction, so educational attainment is not causing PST but PST is causing the reduction of the educational attainment.

NOTE Confidence: 0.852088868618011

00:57:57.940 --> 00:58:01.590 Data are available on Jammer network open so.

NOTE Confidence: 0.903462529182434

00:58:02.250 --> 00:58:17.100 We have a closer relationship, but we are not sure about which is the mechanism because one mechanism could be that educational attainment is a sort of with another mediator, and the manager is actually causing the change in pedia steam.

NOTE Confidence: 0.911139070987701

00:58:18.200 --> 00:58:21.810 So here we have that.

NOTE Confidence: 0.917860507965088

00:58:22.370 --> 00:58:27.820 Different variables can affect this Association for example, risk taking behavior.

NOTE Confidence: 0.888052701950073

00:58:28.350 --> 00:58:59.510 Try my exposure in this case child childhood abuse income could affect the relationship. So we did that multi variable mean that'll organization where we combine this risk factors and see the independence of the effect so the first model includes all the 4th factor and here you can see that risk taking behavior is not changing between them and the Latinization and the multi variable materialization. Same thing for child abuse same thing for income, but for educational attainment.

NOTE Confidence: 0.879787266254425

00:58:59.510 --> 00:59:06.910 We see a change the only valid mental randomization. We have a negative effect when we're just for these other factors.

NOTE Confidence: 0.859786033630371

00:59:07.550 --> 00:59:37.970 They the cows are affected is gone. There isn't anymore. There is something else have explained Association. So we did. Other three models are combining additional payment with the other model Raiders and forest taking behavior. There is no difference child abuse. There is no

difference. But then, when we go to income? Social economic status. We see the big difference, so income. There is not change and we see again a traditional payment only variator there is negative Association adjusted for income.

NOTE Confidence: 0.888364017009735

00:59:37.970 --> 00:59:57.020 The fact is gone so our hypothesis is that they Association between educational attainment. MPST is mediated by income and we did. The other analysis to try and understand what's the biology in the income due was because we're talking about a drivers of income and we can see that there is a difference between.

NOTE Confidence: 0.870939075946808

00:59:57.600 --> 01:00:13.770 Income and educational attainment. Where do they shot me has a much is much more informative for brain relied related mechanism. While income is not that informative so if you want to read the full story. You can go to German network open air written type, so we are still interested.

NOTE Confidence: 0.875486493110657

01:00:14.330 --> 01:00:44.880 In the traditional tainment social anomic status and their relationship. We train 3 different types of these something that Frank is doing and we're put it together a lot of information here about second disorder, externalizing behaviors. Social science outcomes personality traits and brain volumes and we are seeing that. There are differences across second disorder and we're doing them in the lab and opposition Genomic through structural equation modeling Latin castled variance to understand the mechanism a out this relationship.

NOTE Confidence: 0.867745101451874

01:00:44.880 --> 01:01:15.260 Are affecting our risk to develop second disorders and which are these mechanism so this is not published yet and we are working on and we hopefully will poster like a prevalent a few weeks. But I did I really like Mandela randomization and understanding genetic parade so another nice thing to understand for example, is finding biomarkers for trauma response and again. You have out of Environmental Confounders. When you do like an observational study in the in the in.

NOTE Confidence: 0.891928136348724

01:01:15.260 --> 01:01:46.270 A block my own markets. Did you actually measure with respect to gramma response with you? Don't know which is the direction you should? Do Allen Junior study with multiple time points and this means that you need a large amount of resources because you need a large sample size and sometimes you don't have it. So, your sample is small and can be biased bite by other factors. So we use genetic information and we tested 122 metabolites that we're assessing almost 25,000 subjects.

NOTE Confidence: 0.865496158599854

01:01:47.030 --> 01:02:18.620 And thermal response in the UK biobank between 50,000 subjects and 100,000 subjects and we did first genetic correlation analysis and we find that trauma response are different symptoms. Ivo dancer distant being upset after after we are reminded our trauma exposure being irritable rigor thoughts about dramatic experience so all these symptoms. They were assessing the UK biobank through a mental at question are online and so there is some overlap with the.

NOTE Confidence: 0.884805083274841

01:02:18.620 --> 01:02:49.690 At PDS T symptoms, although they are not exactly the same things so we found some genetic correlation. We did our Mandela randomization analysis and we found 3 actually 4. There's one that has like a probably also component of or its interplay gotta be so shared mechanism, so in this case, we have, like only the vertical play geography. Acausal direction and direction is actually this blood metabolites are actually affecting thermal response. We don't we don't see the other way around at least for the.

NOTE Confidence: 0.82976895570755

01:02:49.690 --> 01:03:12.600 For this straight so is the clicker ploy tenacity, Elsa DC trait and the LDL. LDL cholesterol so in 2 cases for GP an illegal broadens ansi trait. We went in the Little and we found evidence in small study about the Association of these metabolites. We traits ready to trauma response like depression anxiety.

NOTE Confidence: 0.869831383228302

01:03:13.720 --> 01:03:44.290 And but these were small study and this was cross sectional study so they'd interval like the ability to distinguish between which is the direction they only reported the Association here. We were showing with genetic information that there is a direction and direction. It is this way. So we have, like a discussion about which may be the mechanism. There is appropriate. Empire Civ so you can read it. If you are interested or asking me questions after that, Alcam but we did also another analysis and we were interest about.

NOTE Confidence: 0.887096107006073

01:03:44.290 --> 01:04:15.450 Computerized device use and securities ordered so everyone is using a Phone or playing with the Phone or play video games. So they are widespread in the population and the result of discussion about which is the effect on mental health and on our behaviors. So we use data from the UK biobank and there's a collision on concerts and and we did first our jet. Correlation analysis and we found a correlation across multiple trades and the strongest one was.

NOTE Confidence: 0.885368049144745

01:04:15.450 --> 01:04:45.780 Between positive or between ADHD an using the

Phone in the the amount of using the Phone in the last 3 months and the playing video games and schizophrenia and Negative Association. So we did again. Our Mandela randomization study and in this case, we didn't find a causal direction. So we found that in both directions. There was an Association. This means that there is horizontal clear that there are mechanisms. There are shared between these 2.

NOTE Confidence: 0.876609563827515

01:04:45.780 --> 01:05:16.260 Part way and that doing like a Richmond analysis and try to understand which is the biology. We found the evidence of dopamine transport and ERD 2 gene for the relationship, the negative relationship between schizophrenia and computer gaming and folks people. The language in in been a positive Association between ADHD and Phone use and in this case so we were also able to do US sex stratify analysis and we observe that is shared mechanism is much stronger in women.

NOTE Confidence: 0.862934052944183

01:05:16.260 --> 01:05:27.320 So we have a lot of hypothesise also about the owner recognition and Fox P2 activity. So if you are interested. We have another program compare type that you can read so.

NOTE Confidence: 0.873424112796783

01:05:28.480 --> 01:05:58.700 Let this is our ratings that we're doing in my lab and we have been rather stuff call with MVP that I cannot show you because I didn't get the authorization. I was late and PC. The Opioid G was that that we are almost done with that, but there are big challenges in Human Genetics. The 1st as I said large sample size. It'll geniti reassessment, but probably the biggest challenge that we have especially because we're seems that we're really close to make an impact on elk are is diversity.

NOTE Confidence: 0.855365574359894

01:05:58.700 --> 01:06:09.350 Here you have did you was reported in that you was catalog and you have different ancestry. Rupert so this blue things European ancestry and then you have the station. The Pinker and then you have other.

NOTE Confidence: 0.861701905727386

01:06:09.870 --> 01:06:41.250 African ancestry is the orangey here and so there is no diversity and we have to derive up originally score from a job was done in European ancestry. In another answer to group you have big issues less power publishing stratification. So if we are making an impact in health care. This means that right now, we're going to to create healthy study other across ethnic groups and here is the analysis, then done by the page study that is our analysis about the US representative.

NOTE Confidence: 0.895567536354065

01:06:41.250 --> 01:07:11.700 Court and you can see how much diversity is these are minority group, so African American Hispanic Asian not evil William Native Americans and even see how much diversity. There is an hour chat mixer. There is so we need to improve our ability to investigate this group switch and focus on device. It goes we need more information, so another thing is the Genomic Revolution is in health care is coming or not so I put this light about the relationship between hype and progress.

NOTE Confidence: 0.874331295490265

01:07:11.700 --> 01:07:42.030 Our things went come out and they are new everyone is excited and in genetics. We are really good to be excited about things. So I counted at least for waves and crash in genetics. Listy before them. Hopefully will not come so the first one, when we started out Jean Kennedy, a social studies. So they were really dining 10 subjects then cases, then controls we found the gene there was a nominal Association and we got the gene. We have it. That's it. They redid it takes over, we found it. We are going to productivity.

NOTE Confidence: 0.904564261436462

01:07:42.030 --> 01:08:13.300 And now we were not able to replicate and, yes, it was not coming so first crush and then there was the human genome project. We sequence, the first human genome at one was so excited billions of dollars is coming. We did now we know everything we are finding everything so that's that's it is fine and then it didn't change anything because we saw. We know we have all the information. Now we have to understand it and it's really complex and then we have the first G was in like they were underpowered.

NOTE Confidence: 0.857135415077209

01:08:13.300 --> 01:08:30.350 And we have the missing readability, but the fridge was was in age. The age rating. Margaret generation and they found the variance with a huge factor as a large balance explain it, I would say OK. That's it. We got it. Now, we are going to work for all these traits and we're going to predict was getting lot.

NOTE Confidence: 0.854371726512909

01:08:30.890 --> 01:08:43.310 Any starting at work, so I crashed again, so people outside genetics. They don't like Geneticists because we we got all the headlines and we get our excited because genetics can have a huge power.

NOTE Confidence: 0.906840085983276

01:08:43.930 --> 01:08:47.150 Potentially, if we are able to crack the mechanism.

NOTE Confidence: 0.81938362121582

01:08:47.930 --> 01:08:49.470 And now we have a general score.

NOTE Confidence: 0.892988562583923

01:08:50.070 --> 01:08:55.940 So everyone is excited again we can predict something we can explain Barry Answer.

NOTE Confidence: 0.898312389850616

01:08:56.780 --> 01:09:20.150 And there is a big discussion of what we're seeing so the variances. I we have the diversity issue. We have bibliography issue. So what you are predicting actually when you put together thousands about it and also how you want to calculate your projected score are you defined threshold. So there are a lot of questions. Also, for example, they emerge project to me like if someone is going to be.

NOTE Confidence: 0.880513668060303

01:09:20.650 --> 01:09:24.800 Can you do these things now you cannot do it? I wrote an entire rant about it and I was saying.

NOTE Confidence: 0.928592145442963

01:09:25.300 --> 01:09:35.510 Let's try this, but it's going to be really, really, really tough is kind of a moon shot because right now, we are not ready for primetime let's stop that.

NOTE Confidence: 0.888833343982697

01:09:36.090 --> 01:09:47.770 When he merged starter will be able to discuss with others and bring together that we will. It may be more than one year to validate the ordinary score because they know? Is one year validation and then 4 years.

NOTE Confidence: 0.914630711078644

01:09:48.420 --> 01:09:52.540 You go and you give the results to the people so I'm not really sure about that.

NOTE Confidence: 0.860634624958038

01:09:53.140 --> 01:10:12.530 So our Commission ready for polygenic medicine my impression. Lee he depends it depends which is usually is it events are our strongest relationship that from with people that do polygenic score analysis and people that do cleaner parties if they have the same people or if they interact alot, yes, they may have the expertise.

NOTE Confidence: 0.855610072612762

01:10:13.030 --> 01:10:31.610 If there isn't this connection people have no idea what up original score is and this is my impression also talked with people that work in different field. They are scientists Super Smart people, but then Paul Italy score? What is apology and rescore? What operation is core does how you calculate it thousands of variants are you select the variance.

NOTE Confidence: 0.92082804441452

01:10:32.440 --> 01:10:44.180 So there are a lot of questions is not is not easy is definitely. I don't help our solution right now, the things is that maybe we should introduce like classes about this stuff.

NOTE Confidence: 0.858255684375763

01:10:44.960 --> 01:11:16.080 Like explaining what is a polygenic score explaining? What is polygyny city that? Yes, you have mutation but most of the variance of the human phenotype and this is explained by tiny effects. So maybe we should improve that so acknowledge Frank Carolina that I didn't mention but you saw the picture that she did some analysis and Guy that just join my group. All obviously all the Funding Agency they gave us money to do some cool stuff and let's do it really, and then all the other people are in the division.

NOTE Confidence: 0.840095400810242

01:11:16.080 --> 01:11:21.640 Human Genetics arejola and all the people that are mostly here, so thank you for the attention.