WEBVTT

NOTE duration: ”00:19:26.250”

NOTE Confidence: 0.9830023

00:00:00.640 --> 00:00:01.680 Yeah. I I had a

NOTE Confidence: 0.9830023

00:00:01.680 --> 00:00:03.139 question, I guess, for Clemens.

NOTE Confidence: 0.9615816

00:00:03.879 --> 00:00:05.920 You know, finding the the

NOTE Confidence: 0.9615816

00:00:05.920 --> 00:00:07.520 the relevant genes under those

NOTE Confidence: 0.9615816

00:00:07.520 --> 00:00:09.440 GWAS peaks is both really

NOTE Confidence: 0.9615816

00:00:09.440 --> 00:00:10.980 important and a challenge.

NOTE Confidence: 0.94727516

00:00:11.759 --> 00:00:13.280 And I was curious about,

NOTE Confidence: 0.94727516

00:00:13.280 --> 00:00:14.014 you you know, with the

NOTE Confidence: 0.94727516

00:00:14.014 --> 00:00:15.934 types of EQTL approaches that

NOTE Confidence: 0.94727516

00:00:15.934 --> 00:00:17.235 you were describing,

NOTE Confidence: 0.99885446

00:00:18.095 --> 00:00:19.875 whether these would pick up,

NOTE Confidence: 0.9541662

00:00:20.335 --> 00:00:22.435 I guess, variants that were

NOTE Confidence: 0.9541662

00:00:22.494 --> 00:00:22.994 conditionally

NOTE Confidence: 0.95207155

00:00:23.295 --> 00:00:24.915 dependent. Like, for example,

NOTE Confidence: 0.9982522

00:00:25.530 --> 00:00:26.970 you know, a variant that

NOTE Confidence: 0.9982522

00:00:26.970 --> 00:00:28.110 might be really important

NOTE Confidence: 0.9974405

00:00:28.570 --> 00:00:29.690 if you happen to be

NOTE Confidence: 0.98330146

00:00:30.410 --> 00:00:31.450 you know, have had a

NOTE Confidence: 0.98330146

00:00:31.450 --> 00:00:33.050 stroke or have been, you

NOTE Confidence: 0.98330146

00:00:33.050 --> 00:00:34.890 know, infected with a virus,

NOTE Confidence: 0.98330146

00:00:34.890 --> 00:00:35.850 but might be hard to

NOTE Confidence: 0.98330146

00:00:35.850 --> 00:00:37.530 capture just with thousands of

NOTE Confidence: 0.98330146

00:00:37.530 --> 00:00:38.409 samples out of a, you

NOTE Confidence: 0.98330146

00:00:38.409 --> 00:00:39.950 know, sort of random population.

NOTE Confidence: 0.98330146

00:00:40.250 --> 00:00:41.705 Yeah. Is so, I guess,

NOTE Confidence: 0.98330146

00:00:41.705 --> 00:00:42.665 how well does this type

NOTE Confidence: 0.98330146

00:00:42.665 --> 00:00:43.865 of analysis deal with that,

NOTE Confidence: 0.98330146

00:00:43.865 --> 00:00:44.745 and is there a way

NOTE Confidence: 0.98330146

00:00:44.745 --> 00:00:46.025 to somehow take into account

NOTE Confidence: 0.98330146

00:00:46.025 --> 00:00:47.085 these extra variables?

NOTE Confidence: 0.912426

00:00:47.625 --> 00:00:49.065 Right. So so this is

NOTE Confidence: 0.912426

00:00:49.065 --> 00:00:51.165 a very exciting avenue that,

NOTE Confidence: 0.828414

00:00:52.840 --> 00:00:54.220 Zetsu and Lin, an instructor

NOTE Confidence: 0.828414

00:00:54.280 --> 00:00:55.080 in the lab and I

NOTE Confidence: 0.828414

00:00:55.080 --> 00:00:57.080 am very interested in, and

NOTE Confidence: 0.828414

00:00:57.080 --> 00:00:58.200 and sort of it goes,

NOTE Confidence: 0.828414

00:00:58.200 --> 00:00:59.100 is there any

NOTE Confidence: 0.9529898

00:00:59.880 --> 00:01:00.620 are there,

NOTE Confidence: 0.86283386

00:01:01.160 --> 00:01:01.660 loci

NOTE Confidence: 0.96657896

00:01:02.840 --> 00:01:03.340 that,

NOTE Confidence: 0.9412736

00:01:03.800 --> 00:01:04.300 are

NOTE Confidence: 0.95090663

00:01:05.095 --> 00:01:07.034 react to to pathology

NOTE Confidence: 0.9108701

00:01:07.334 --> 00:01:08.455 in in the brain. And

NOTE Confidence: 0.9108701

00:01:08.455 --> 00:01:10.055 we we've been focused so

NOTE Confidence: 0.9108701

00:01:10.055 --> 00:01:11.595 far really on loci

NOTE Confidence: 0.9831322

00:01:12.215 --> 00:01:14.535 quantitative trait loci that might

NOTE Confidence: 0.9831322

00:01:14.535 --> 00:01:15.895 be turned on or turned

NOTE Confidence: 0.9831322

00:01:15.895 --> 00:01:16.395 off,

NOTE Confidence: 0.9340788

00:01:19.020 --> 00:01:20.399 by Lewy body pathology.

NOTE Confidence: 0.9988827

00:01:21.259 --> 00:01:21.759 And

NOTE Confidence: 0.9893681

00:01:22.299 --> 00:01:23.920 and and so for our

NOTE Confidence: 0.9971466

00:01:24.459 --> 00:01:24.959 Parkinson's

NOTE Confidence: 0.94842595

00:01:25.579 --> 00:01:26.939 p d five d, you

NOTE Confidence: 0.94842595

00:01:26.939 --> 00:01:28.860 know, digital twin approach, so

NOTE Confidence: 0.94842595

00:01:28.860 --> 00:01:30.539 we're looking at Parkinson's brains.

NOTE Confidence: 0.94842595

00:01:30.539 --> 00:01:31.899 We we have the Lewy

NOTE Confidence: 0.94842595

00:01:31.899 --> 00:01:32.399 body

NOTE Confidence: 0.92166984

00:01:32.865 --> 00:01:34.225 pathology with the plaques and

NOTE Confidence: 0.92166984

00:01:34.225 --> 00:01:34.805 the tangles.

NOTE Confidence: 0.8794816

00:01:35.265 --> 00:01:36.645 We actually so

NOTE Confidence: 0.96609485

00:01:37.185 --> 00:01:38.705 so far, we've only found

NOTE Confidence: 0.96609485

00:01:38.705 --> 00:01:39.285 a few,

NOTE Confidence: 0.91617835

00:01:40.305 --> 00:01:42.065 target genes, but there's a

NOTE Confidence: 0.91617835

00:01:42.065 --> 00:01:42.805 clear interaction

NOTE Confidence: 0.9860694

00:01:43.265 --> 00:01:45.205 with Lewy body pathology. Interestingly,

NOTE Confidence: 0.9413152

00:01:45.730 --> 00:01:47.170 PM twenty d one,

NOTE Confidence: 0.9012248

00:01:47.570 --> 00:01:49.090 was one of the few

NOTE Confidence: 0.9012248

00:01:49.090 --> 00:01:49.590 genes

NOTE Confidence: 0.9489878

00:01:50.130 --> 00:01:50.630 where,

NOTE Confidence: 0.97462845

00:01:52.050 --> 00:01:53.830 Lewy body pathology actually,

NOTE Confidence: 0.9509014

00:01:54.370 --> 00:01:56.070 turned off the the regulatory

NOTE Confidence: 0.9509014

00:01:56.210 --> 00:01:57.890 f effects. So so there

NOTE Confidence: 0.9509014

00:01:57.890 --> 00:01:59.625 are some effects we're very

NOTE Confidence: 0.9509014

00:01:59.625 --> 00:02:00.825 interested in. There's much more

NOTE Confidence: 0.9509014

00:02:00.825 --> 00:02:01.725 to do, and,

NOTE Confidence: 0.9614946

00:02:02.665 --> 00:02:03.865 look forward to chat chat

NOTE Confidence: 0.9614946

00:02:03.865 --> 00:02:04.845 more with him.

NOTE Confidence: 0.45579004

00:02:06.345 --> 00:02:06.845 See,

NOTE Confidence: 0.89026004

00:02:08.264 --> 00:02:09.805 maybe as a follow-up question?

NOTE Confidence: 0.6818036

00:02:12.440 --> 00:02:13.340 Yeah. It

NOTE Confidence: 0.8290949

00:02:13.880 --> 00:02:14.380 worked.

NOTE Confidence: 0.75287724

00:02:14.919 --> 00:02:16.620 Yes. I follow-up follow-up question

NOTE Confidence: 0.75287724

00:02:16.680 --> 00:02:17.500 to Sean's question.

NOTE Confidence: 0.96584153

00:02:19.880 --> 00:02:20.760 What do you think is

NOTE Confidence: 0.96584153

00:02:20.760 --> 00:02:22.060 needed in terms of genomics

NOTE Confidence: 0.96584153

00:02:22.120 --> 00:02:22.860 to distinguish

NOTE Confidence: 0.99948305

00:02:24.465 --> 00:02:25.764 risk factors for onset

NOTE Confidence: 0.97996193

00:02:26.065 --> 00:02:27.605 and risk factors for progression?

NOTE Confidence: 0.97996193

00:02:27.665 --> 00:02:28.945 Because I've obviously, for the

NOTE Confidence: 0.97996193

00:02:28.945 --> 00:02:30.645 patients, if one has interventions

NOTE Confidence: 0.97996193

00:02:30.785 --> 00:02:32.145 for progression, you probably can

NOTE Confidence: 0.97996193

00:02:32.145 --> 00:02:33.185 save one third or half

NOTE Confidence: 0.97996193

00:02:33.185 --> 00:02:34.625 of the people that way

NOTE Confidence: 0.97996193

00:02:34.625 --> 00:02:35.985 because it's such a long

NOTE Confidence: 0.97996193

00:02:35.985 --> 00:02:36.485 duration.

NOTE Confidence: 0.84096146

00:02:37.360 --> 00:02:38.100 But you explained

NOTE Confidence: 0.975305

00:02:38.720 --> 00:02:40.800 access to patient data with,

NOTE Confidence: 0.975305

00:02:41.280 --> 00:02:42.180 early onset.

NOTE Confidence: 0.98499143

00:02:42.480 --> 00:02:44.320 But, is that sufficient, or

NOTE Confidence: 0.98499143

00:02:44.320 --> 00:02:45.520 do we need other type

NOTE Confidence: 0.98499143

00:02:45.520 --> 00:02:47.460 of genomics information to

NOTE Confidence: 0.99877393

00:02:47.760 --> 00:02:49.780 better distinguish these two factors?

NOTE Confidence: 0.99023783

00:02:50.115 --> 00:02:51.155 Right. So,

NOTE Confidence: 0.9696525

00:02:51.955 --> 00:02:53.555 didn't have a chance to

NOTE Confidence: 0.9696525

00:02:53.555 --> 00:02:55.075 talk about this. I'll touch

NOTE Confidence: 0.9696525

00:02:55.075 --> 00:02:55.955 up on this at the

NOTE Confidence: 0.9696525

00:02:55.955 --> 00:02:57.095 very end of the symposium.

NOTE Confidence: 0.98157203

00:02:57.555 --> 00:02:57.875 But,

NOTE Confidence: 0.9048851

00:02:58.355 --> 00:02:58.855 so,

NOTE Confidence: 0.9955047

00:02:59.875 --> 00:03:00.375 actually,

NOTE Confidence: 0.9927379

00:03:01.075 --> 00:03:03.014 we're very proud to

NOTE Confidence: 0.9539349

00:03:03.910 --> 00:03:05.430 really, in a way, have

NOTE Confidence: 0.9539349

00:03:05.430 --> 00:03:06.630 opened up the field of

NOTE Confidence: 0.9539349

00:03:06.630 --> 00:03:07.130 progression,

NOTE Confidence: 0.8996912

00:03:07.590 --> 00:03:08.090 genetics,

NOTE Confidence: 0.98628545

00:03:08.710 --> 00:03:09.210 or

NOTE Confidence: 0.95811486

00:03:09.910 --> 00:03:11.050 neurologic diseases.

NOTE Confidence: 0.99643433

00:03:11.590 --> 00:03:12.810 And so on that

NOTE Confidence: 0.8981093

00:03:13.830 --> 00:03:15.110 one slide that I showed,

NOTE Confidence: 0.8981093

00:03:15.110 --> 00:03:16.875 there actually the dimension of

NOTE Confidence: 0.8981093

00:03:17.035 --> 00:03:18.235 of of risk and the

NOTE Confidence: 0.8981093

00:03:18.235 --> 00:03:19.615 dimension of progression.

NOTE Confidence: 0.975125

00:03:20.475 --> 00:03:21.695 And turns out

NOTE Confidence: 0.9129154

00:03:23.195 --> 00:03:24.794 there's there's some variants that

NOTE Confidence: 0.9129154

00:03:24.794 --> 00:03:26.555 regulate onset and progression, but

NOTE Confidence: 0.9129154

00:03:26.555 --> 00:03:27.675 then there was some variants

NOTE Confidence: 0.9129154

00:03:27.675 --> 00:03:29.275 that just regulate progression and

NOTE Confidence: 0.9129154

00:03:29.275 --> 00:03:30.260 others just,

NOTE Confidence: 0.99701774

00:03:30.739 --> 00:03:31.560 just risk.

NOTE Confidence: 0.9659488

00:03:32.260 --> 00:03:33.560 And and so,

NOTE Confidence: 0.8933318

00:03:35.220 --> 00:03:36.660 at the Adam Center, we

NOTE Confidence: 0.8933318

00:03:36.660 --> 00:03:38.260 are, in in this,

NOTE Confidence: 0.97683287

00:03:39.300 --> 00:03:39.800 multilayered,

NOTE Confidence: 0.9356165

00:03:41.060 --> 00:03:42.739 you know, Parkinson's Atlas or

NOTE Confidence: 0.9356165

00:03:42.739 --> 00:03:44.040 digital twin of Parkinson's.

NOTE Confidence: 0.9976719

00:03:44.435 --> 00:03:45.495 We are including,

NOTE Confidence: 0.9994332

00:03:46.194 --> 00:03:47.254 the time component

NOTE Confidence: 0.9149058

00:03:47.795 --> 00:03:49.155 both in terms of we

NOTE Confidence: 0.9149058

00:03:49.155 --> 00:03:50.534 have, ten thousand,

NOTE Confidence: 0.983451

00:03:52.114 --> 00:03:52.614 longitudinal

NOTE Confidence: 0.89817524

00:03:52.995 --> 00:03:54.834 life patient cohorts where where

NOTE Confidence: 0.89817524

00:03:54.834 --> 00:03:56.775 we have longitudinal clinical data.

NOTE Confidence: 0.89817524

00:03:56.995 --> 00:03:58.215 And then on the pathology

NOTE Confidence: 0.89817524

00:03:58.355 --> 00:03:59.580 level, you know, we have

NOTE Confidence: 0.89817524

00:03:59.580 --> 00:04:01.660 to serious from on onset

NOTE Confidence: 0.89817524

00:04:01.660 --> 00:04:03.500 to progression. So so, yes,

NOTE Confidence: 0.89817524

00:04:03.500 --> 00:04:04.460 so this, I think, is

NOTE Confidence: 0.89817524

00:04:04.460 --> 00:04:05.840 a very interesting question,

NOTE Confidence: 0.9517737

00:04:06.620 --> 00:04:08.460 much to do, but we

NOTE Confidence: 0.9517737

00:04:08.460 --> 00:04:09.200 are we're

NOTE Confidence: 0.9972567

00:04:09.580 --> 00:04:11.100 we're building the platforms to

NOTE Confidence: 0.9972567

00:04:11.100 --> 00:04:11.760 do it.

NOTE Confidence: 0.9629499

00:04:17.605 --> 00:04:19.125 Oh, okay. Just a question

NOTE Confidence: 0.9629499

00:04:19.125 --> 00:04:20.425 for doctor Strippmatter.

NOTE Confidence: 0.91787934

00:04:21.045 --> 00:04:22.505 So right over here.

NOTE Confidence: 0.9970789

00:04:22.964 --> 00:04:23.785 Other side.

NOTE Confidence: 0.7567517

00:04:24.404 --> 00:04:26.729 Hi. Angela Kacasi, Arvinis.

NOTE Confidence: 0.8959334

00:04:27.110 --> 00:04:28.949 My question is about, per

NOTE Confidence: 0.8959334

00:04:28.949 --> 00:04:29.449 granuline

NOTE Confidence: 0.9933734

00:04:29.830 --> 00:04:31.770 reduction and how that impacts

NOTE Confidence: 0.9538267

00:04:32.470 --> 00:04:34.630 the aggregates that that form

NOTE Confidence: 0.9538267

00:04:34.630 --> 00:04:35.529 that are insoluble.

NOTE Confidence: 0.99563724

00:04:36.229 --> 00:04:37.770 And then you also mentioned

NOTE Confidence: 0.99563724

00:04:37.830 --> 00:04:39.529 that this rescues function

NOTE Confidence: 0.94184524

00:04:40.265 --> 00:04:42.125 and improves the damn microglia

NOTE Confidence: 0.94184524

00:04:42.265 --> 00:04:43.404 phenotype, etcetera.

NOTE Confidence: 0.9981254

00:04:44.025 --> 00:04:45.464 Do you believe that there's

NOTE Confidence: 0.9981254

00:04:45.464 --> 00:04:46.285 a biomarker

NOTE Confidence: 0.9940558

00:04:46.585 --> 00:04:48.045 for that type of soluble

NOTE Confidence: 0.9940558

00:04:48.185 --> 00:04:49.464 oligomer of tau that you

NOTE Confidence: 0.9940558

00:04:49.464 --> 00:04:51.085 think is causing the dysfunction

NOTE Confidence: 0.93246424

00:04:51.705 --> 00:04:53.165 that might be really meaningful,

NOTE Confidence: 0.991161

00:04:54.340 --> 00:04:56.420 to really assess when you're

NOTE Confidence: 0.991161

00:04:56.420 --> 00:04:58.360 perturbing lysosome dysfunction.

NOTE Confidence: 0.9491114

00:04:58.820 --> 00:04:59.940 We have a LARC two

NOTE Confidence: 0.9491114

00:04:59.940 --> 00:05:01.620 PROTAC that we're just going

NOTE Confidence: 0.9491114

00:05:01.620 --> 00:05:02.920 to talk about at ADPD

NOTE Confidence: 0.9491114

00:05:03.060 --> 00:05:04.660 next week, where we see

NOTE Confidence: 0.9491114

00:05:04.660 --> 00:05:06.440 reductions in soluble oligomers.

NOTE Confidence: 0.92215365

00:05:07.235 --> 00:05:08.435 We know we're impacting the

NOTE Confidence: 0.92215365

00:05:08.435 --> 00:05:09.654 lysosome system,

NOTE Confidence: 0.9926521

00:05:09.955 --> 00:05:11.315 but we're not impacting the

NOTE Confidence: 0.9926521

00:05:11.315 --> 00:05:13.154 insoluble tau fraction. So we

NOTE Confidence: 0.9926521

00:05:13.154 --> 00:05:14.435 think this would be really

NOTE Confidence: 0.9926521

00:05:14.435 --> 00:05:14.935 interesting

NOTE Confidence: 0.9874573

00:05:15.395 --> 00:05:16.935 to study in human disease,

NOTE Confidence: 0.9963912

00:05:17.235 --> 00:05:18.595 but we're interested in your

NOTE Confidence: 0.9963912

00:05:18.595 --> 00:05:19.795 insights on how would you

NOTE Confidence: 0.9963912

00:05:19.795 --> 00:05:21.015 go about doing that.

NOTE Confidence: 0.95387423

00:05:22.120 --> 00:05:23.720 Yeah. I think those data

NOTE Confidence: 0.95387423

00:05:23.720 --> 00:05:25.880 certainly you know, the simplest

NOTE Confidence: 0.95387423

00:05:25.880 --> 00:05:26.839 model is there's a one

NOTE Confidence: 0.95387423

00:05:26.839 --> 00:05:29.100 to one correlation between aggregation

NOTE Confidence: 0.94945794

00:05:29.800 --> 00:05:31.560 and disease, but it's I

NOTE Confidence: 0.94945794

00:05:31.560 --> 00:05:33.000 think these data amongst many

NOTE Confidence: 0.94945794

00:05:33.000 --> 00:05:34.759 others prove that that's not

NOTE Confidence: 0.94945794

00:05:34.759 --> 00:05:35.385 the case.

NOTE Confidence: 0.96601766

00:05:35.785 --> 00:05:37.385 And so as you're pointing

NOTE Confidence: 0.96601766

00:05:37.385 --> 00:05:37.885 out,

NOTE Confidence: 0.99854344

00:05:38.585 --> 00:05:40.525 understanding whether there's different

NOTE Confidence: 0.99359334

00:05:41.865 --> 00:05:44.445 types of misfolding, different aggregates,

NOTE Confidence: 0.994972

00:05:45.785 --> 00:05:47.145 and which ones are most

NOTE Confidence: 0.994972

00:05:47.145 --> 00:05:48.585 important for disease is an

NOTE Confidence: 0.994972

00:05:48.585 --> 00:05:49.565 important question.

NOTE Confidence: 0.9908575

00:05:50.120 --> 00:05:51.640 This may be one handle

NOTE Confidence: 0.9908575

00:05:51.640 --> 00:05:53.320 on getting at that by

NOTE Confidence: 0.9908575

00:05:53.320 --> 00:05:53.820 studying,

NOTE Confidence: 0.9685569

00:05:54.200 --> 00:05:54.940 these animals.

NOTE Confidence: 0.98070604

00:05:56.920 --> 00:05:57.800 But I think, you know,

NOTE Confidence: 0.98070604

00:05:57.800 --> 00:05:58.680 the short answer is we

NOTE Confidence: 0.98070604

00:05:58.680 --> 00:05:59.880 don't know what are the

NOTE Confidence: 0.98070604

00:05:59.880 --> 00:06:00.700 most relevant

NOTE Confidence: 0.9870461

00:06:02.305 --> 00:06:04.324 toxic species of misfolded

NOTE Confidence: 0.99252045

00:06:04.625 --> 00:06:05.125 neurodegenerative

NOTE Confidence: 0.8595772

00:06:05.664 --> 00:06:06.164 proteins.

NOTE Confidence: 0.9756016

00:06:11.504 --> 00:06:12.705 Hi. This is a question

NOTE Confidence: 0.9756016

00:06:12.705 --> 00:06:14.145 that piggybacks off the first

NOTE Confidence: 0.9756016

00:06:14.145 --> 00:06:14.645 two.

NOTE Confidence: 0.9606459

00:06:15.264 --> 00:06:16.004 And maybe,

NOTE Confidence: 0.8218385

00:06:16.380 --> 00:06:17.120 doctor Liu,

NOTE Confidence: 0.94221437

00:06:17.580 --> 00:06:19.600 specifically, you mentioned missing heritability.

NOTE Confidence: 0.95311236

00:06:20.220 --> 00:06:21.580 And, certainly, there's, a lot

NOTE Confidence: 0.95311236

00:06:21.580 --> 00:06:22.540 of people in the Parkinson's

NOTE Confidence: 0.95311236

00:06:22.540 --> 00:06:23.980 field that feel that there

NOTE Confidence: 0.95311236

00:06:23.980 --> 00:06:25.740 isn't missing heritability. It's really

NOTE Confidence: 0.95311236

00:06:25.740 --> 00:06:27.680 environment. That's, that's the huge,

NOTE Confidence: 0.9513525

00:06:28.775 --> 00:06:29.654 sort of elephant in the

NOTE Confidence: 0.9513525

00:06:29.654 --> 00:06:31.095 room, and that could mean

NOTE Confidence: 0.9513525

00:06:31.095 --> 00:06:32.455 exposure to paraquat, which has

NOTE Confidence: 0.9513525

00:06:32.455 --> 00:06:33.815 talked about a tremendous amount

NOTE Confidence: 0.9513525

00:06:33.815 --> 00:06:35.495 in the advocacy world versus,

NOTE Confidence: 0.9513525

00:06:35.495 --> 00:06:37.095 you know, exercise, exposure to

NOTE Confidence: 0.9513525

00:06:37.095 --> 00:06:37.595 coffee,

NOTE Confidence: 0.8267632

00:06:38.214 --> 00:06:39.275 huge list. So,

NOTE Confidence: 0.9840635

00:06:39.735 --> 00:06:41.575 that's that's a huge undertaking,

NOTE Confidence: 0.9840635

00:06:41.575 --> 00:06:43.240 and I wonder how that's

NOTE Confidence: 0.9840635

00:06:43.240 --> 00:06:44.520 sort of feeding into many

NOTE Confidence: 0.9840635

00:06:44.520 --> 00:06:46.120 of your models. Sure. Yeah.

NOTE Confidence: 0.9840635

00:06:46.120 --> 00:06:47.000 No. Thank you for that

NOTE Confidence: 0.9840635

00:06:47.000 --> 00:06:48.520 question. You know, the the

NOTE Confidence: 0.9840635

00:06:48.520 --> 00:06:49.960 question of missing heritability is

NOTE Confidence: 0.9840635

00:06:49.960 --> 00:06:51.080 always hard because it's it's

NOTE Confidence: 0.9840635

00:06:51.080 --> 00:06:52.440 the unknown. And and you

NOTE Confidence: 0.9840635

00:06:52.440 --> 00:06:53.420 mentioned environment.

NOTE Confidence: 0.99053276

00:06:54.279 --> 00:06:55.735 So when we when we

NOTE Confidence: 0.99053276

00:06:55.735 --> 00:06:57.015 try to capture the missing

NOTE Confidence: 0.99053276

00:06:57.015 --> 00:06:59.035 heritability using these wearable devices,

NOTE Confidence: 0.98441297

00:06:59.335 --> 00:07:00.455 it could be the case

NOTE Confidence: 0.98441297

00:07:00.455 --> 00:07:02.695 that these devices are actually

NOTE Confidence: 0.98441297

00:07:02.695 --> 00:07:04.555 capturing something about the environment,

NOTE Confidence: 0.9990994

00:07:05.095 --> 00:07:05.835 for example,

NOTE Confidence: 0.9979906

00:07:06.695 --> 00:07:07.675 response to stimuli.

NOTE Confidence: 0.9772851

00:07:08.375 --> 00:07:09.415 So the lines get kind

NOTE Confidence: 0.9772851

00:07:09.415 --> 00:07:11.020 of blurred between what the

NOTE Confidence: 0.9772851

00:07:11.020 --> 00:07:12.540 missing heritability is versus what

NOTE Confidence: 0.9772851

00:07:12.540 --> 00:07:14.220 the environment is. But the

NOTE Confidence: 0.9772851

00:07:14.220 --> 00:07:15.260 good thing I think there

NOTE Confidence: 0.9772851

00:07:15.260 --> 00:07:17.419 is using these devices, like

NOTE Confidence: 0.9772851

00:07:17.419 --> 00:07:18.560 wearables and smartwatches,

NOTE Confidence: 0.99979764

00:07:19.180 --> 00:07:20.800 they are measuring continuously

NOTE Confidence: 0.9960774

00:07:21.580 --> 00:07:23.120 as someone kind of interacts,

NOTE Confidence: 0.99862385

00:07:23.660 --> 00:07:25.180 through their environment and with

NOTE Confidence: 0.99862385

00:07:25.180 --> 00:07:26.794 their environment. And so I

NOTE Confidence: 0.99862385

00:07:26.794 --> 00:07:27.935 I do think that

NOTE Confidence: 0.95678365

00:07:28.794 --> 00:07:30.895 by using such devices, unlike

NOTE Confidence: 0.92824996

00:07:31.354 --> 00:07:33.035 other technologies which only measure

NOTE Confidence: 0.92824996

00:07:33.035 --> 00:07:34.715 one time point, we're we're

NOTE Confidence: 0.92824996

00:07:34.715 --> 00:07:36.335 really actually able to capture,

NOTE Confidence: 0.98605

00:07:37.275 --> 00:07:38.574 much more of that environmental

NOTE Confidence: 0.98605

00:07:38.635 --> 00:07:39.900 effect. And I hope that,

NOTE Confidence: 0.98605

00:07:40.220 --> 00:07:41.740 things like Parkinson's can be

NOTE Confidence: 0.98605

00:07:41.740 --> 00:07:42.560 better characterized,

NOTE Confidence: 0.99980605

00:07:43.259 --> 00:07:44.880 through devices like this.

NOTE Confidence: 0.9618848

00:07:47.660 --> 00:07:49.020 Yeah. I have a question

NOTE Confidence: 0.9618848

00:07:49.020 --> 00:07:50.479 on the circular RNA

NOTE Confidence: 0.88353926

00:07:50.780 --> 00:07:52.960 that you discuss. Circular RNA.

NOTE Confidence: 0.88353926

00:07:53.020 --> 00:07:53.520 Yeah.

NOTE Confidence: 0.92467284

00:07:54.055 --> 00:07:55.175 Yeah. You say that there

NOTE Confidence: 0.92467284

00:07:55.175 --> 00:07:56.715 was an increase in particular

NOTE Confidence: 0.92467284

00:07:56.935 --> 00:07:58.935 or certain circular RNA in

NOTE Confidence: 0.92467284

00:07:58.935 --> 00:08:00.075 Parkinson disease.

NOTE Confidence: 0.9662171

00:08:00.775 --> 00:08:01.095 And,

NOTE Confidence: 0.9672493

00:08:01.735 --> 00:08:03.014 I thought do you see

NOTE Confidence: 0.9672493

00:08:03.014 --> 00:08:05.275 them as upstream or downstream

NOTE Confidence: 0.9672493

00:08:05.415 --> 00:08:05.915 of

NOTE Confidence: 0.7484312

00:08:06.310 --> 00:08:06.810 Parkinson's,

NOTE Confidence: 0.9833334

00:08:07.990 --> 00:08:09.430 phenotype? Because you say that

NOTE Confidence: 0.9833334

00:08:09.430 --> 00:08:11.610 you were thinking of treating,

NOTE Confidence: 0.9066178

00:08:13.509 --> 00:08:15.669 cells with circular RNA to

NOTE Confidence: 0.9066178

00:08:15.669 --> 00:08:16.889 see whether you rescue

NOTE Confidence: 0.8690785

00:08:17.350 --> 00:08:18.009 the Parkinson's.

NOTE Confidence: 0.9385386

00:08:18.310 --> 00:08:19.669 So it's unclear to me

NOTE Confidence: 0.9385386

00:08:19.669 --> 00:08:20.710 where you put them in

NOTE Confidence: 0.9385386

00:08:20.710 --> 00:08:21.210 the

NOTE Confidence: 0.92977965

00:08:21.535 --> 00:08:23.295 sequence of event. I think

NOTE Confidence: 0.92977965

00:08:23.295 --> 00:08:25.295 it's unclear to me too

NOTE Confidence: 0.92977965

00:08:25.295 --> 00:08:26.915 whether it's upstream or downstream.

NOTE Confidence: 0.89360046

00:08:27.775 --> 00:08:29.315 We do this is association

NOTE Confidence: 0.89360046

00:08:29.535 --> 00:08:31.135 study based the the published

NOTE Confidence: 0.89360046

00:08:31.135 --> 00:08:32.434 one, but

NOTE Confidence: 0.9714825

00:08:32.975 --> 00:08:33.715 my personal

NOTE Confidence: 0.9428621

00:08:35.830 --> 00:08:37.270 hypothesis there, it could be

NOTE Confidence: 0.9428621

00:08:37.270 --> 00:08:37.770 upstream.

NOTE Confidence: 0.8920284

00:08:38.710 --> 00:08:40.950 Why I think circular RNA,

NOTE Confidence: 0.8920284

00:08:40.950 --> 00:08:42.230 most of them don't translate

NOTE Confidence: 0.8920284

00:08:42.230 --> 00:08:42.890 to protein.

NOTE Confidence: 0.8779297

00:08:43.350 --> 00:08:44.470 But that but why they

NOTE Confidence: 0.8779297

00:08:44.470 --> 00:08:44.870 are,

NOTE Confidence: 0.9281455

00:08:45.429 --> 00:08:47.510 transport and enriching synapses, they

NOTE Confidence: 0.9281455

00:08:47.510 --> 00:08:48.675 must play a role there.

NOTE Confidence: 0.94597995

00:08:49.154 --> 00:08:50.515 Whether they function as RNA

NOTE Confidence: 0.94597995

00:08:50.515 --> 00:08:52.355 binding protein, like, help the

NOTE Confidence: 0.94597995

00:08:52.355 --> 00:08:54.755 transportation of other messenger RNA

NOTE Confidence: 0.94597995

00:08:54.755 --> 00:08:55.654 to the synapses

NOTE Confidence: 0.8670462

00:08:56.274 --> 00:08:57.714 because the local translation center

NOTE Confidence: 0.8670462

00:08:57.714 --> 00:08:58.675 in the synapses, as you

NOTE Confidence: 0.8670462

00:08:58.675 --> 00:08:59.175 know.

NOTE Confidence: 0.4031168

00:08:59.955 --> 00:09:00.455 Whether

NOTE Confidence: 0.9182038

00:09:01.130 --> 00:09:03.050 and, also, the known function

NOTE Confidence: 0.9182038

00:09:03.050 --> 00:09:05.050 for other, circular RNA, people

NOTE Confidence: 0.9182038

00:09:05.050 --> 00:09:06.830 show RNA binding protein,

NOTE Confidence: 0.8781927

00:09:07.290 --> 00:09:08.809 like and muscle blind, for

NOTE Confidence: 0.8781927

00:09:08.809 --> 00:09:10.250 example, a good example published

NOTE Confidence: 0.8781927

00:09:10.250 --> 00:09:12.410 already. This microRNA sponge can

NOTE Confidence: 0.8781927

00:09:12.410 --> 00:09:13.790 be another mere seven,

NOTE Confidence: 0.8989457

00:09:14.465 --> 00:09:16.165 like, the the first circulary

NOTE Confidence: 0.8989457

00:09:16.304 --> 00:09:17.585 defined in two thousand seven

NOTE Confidence: 0.8989457

00:09:18.065 --> 00:09:19.745 fourteen was c dot one

NOTE Confidence: 0.8989457

00:09:19.745 --> 00:09:21.445 a s. They have seventy,

NOTE Confidence: 0.9164269

00:09:21.985 --> 00:09:23.585 miR seven binding sites there.

NOTE Confidence: 0.9164269

00:09:23.585 --> 00:09:24.545 So it's like a sponge

NOTE Confidence: 0.9164269

00:09:24.545 --> 00:09:25.905 to release and solve miR

NOTE Confidence: 0.9164269

00:09:25.905 --> 00:09:27.184 seven. MiR seven controls the

NOTE Confidence: 0.9164269

00:09:27.184 --> 00:09:29.250 nuclei. So this is already

NOTE Confidence: 0.9164269

00:09:29.250 --> 00:09:31.029 kind of known pathway

NOTE Confidence: 0.7925742

00:09:31.410 --> 00:09:33.090 from circulating to macronally to

NOTE Confidence: 0.7925742

00:09:33.090 --> 00:09:33.590 snooply.

NOTE Confidence: 0.89461535

00:09:34.130 --> 00:09:35.490 But how this link to

NOTE Confidence: 0.89461535

00:09:35.490 --> 00:09:37.250 synapses, that's really something I

NOTE Confidence: 0.89461535

00:09:37.250 --> 00:09:38.529 mean, synuclein is part of

NOTE Confidence: 0.89461535

00:09:38.529 --> 00:09:39.110 the synapses,

NOTE Confidence: 0.85566777

00:09:39.570 --> 00:09:41.910 snare pathway. But how this

NOTE Confidence: 0.85566777

00:09:42.050 --> 00:09:43.429 caused the the synaptic

NOTE Confidence: 0.9284995

00:09:43.944 --> 00:09:44.444 disruption,

NOTE Confidence: 0.89790285

00:09:45.144 --> 00:09:46.584 I I don't have data.

NOTE Confidence: 0.89790285

00:09:46.584 --> 00:09:47.865 But this is I think

NOTE Confidence: 0.89790285

00:09:47.865 --> 00:09:50.105 it's just my, hypothesis. I

NOTE Confidence: 0.89790285

00:09:50.105 --> 00:09:51.225 think it's more likely to

NOTE Confidence: 0.89790285

00:09:51.225 --> 00:09:51.964 be upstream.

NOTE Confidence: 0.9372781

00:09:57.420 --> 00:09:57.920 I

NOTE Confidence: 0.94216764

00:09:59.019 --> 00:10:00.059 I would like to ask

NOTE Confidence: 0.94216764

00:10:00.059 --> 00:10:01.839 a question to Pablo Sardi

NOTE Confidence: 0.94216764

00:10:01.899 --> 00:10:02.720 in the audience,

NOTE Confidence: 0.9997192

00:10:03.179 --> 00:10:03.679 who

NOTE Confidence: 0.83816785

00:10:04.059 --> 00:10:05.360 is the head of,

NOTE Confidence: 0.9842754

00:10:06.059 --> 00:10:08.220 rare and neurologic disease research

NOTE Confidence: 0.9842754

00:10:08.220 --> 00:10:08.880 at Sanofi.

NOTE Confidence: 0.9949586

00:10:09.339 --> 00:10:11.040 Pablo, I know you have

NOTE Confidence: 0.99371934

00:10:11.605 --> 00:10:13.225 a deep pipeline around,

NOTE Confidence: 0.9056179

00:10:14.085 --> 00:10:16.665 GBA, GC, GKs, drugs,

NOTE Confidence: 0.87391764

00:10:17.925 --> 00:10:19.705 in Gaucher disease and Parkinson's

NOTE Confidence: 0.87391764

00:10:19.925 --> 00:10:20.425 disease.

NOTE Confidence: 0.98805946

00:10:20.965 --> 00:10:21.925 And and so I was

NOTE Confidence: 0.98805946

00:10:21.925 --> 00:10:23.625 very curious what your reaction

NOTE Confidence: 0.98805946

00:10:23.845 --> 00:10:25.145 was to the data,

NOTE Confidence: 0.78086877

00:10:26.070 --> 00:10:26.970 Steven showed,

NOTE Confidence: 0.9781685

00:10:28.470 --> 00:10:28.970 about,

NOTE Confidence: 0.7048357

00:10:30.230 --> 00:10:31.930 galactos ceramide and,

NOTE Confidence: 0.96698153

00:10:32.710 --> 00:10:33.210 neurofibrillary

NOTE Confidence: 0.9691184

00:10:33.590 --> 00:10:34.090 tangles.

NOTE Confidence: 0.9023082

00:10:35.990 --> 00:10:37.350 This is supposed to work

NOTE Confidence: 0.9023082

00:10:37.350 --> 00:10:38.390 the other way around where

NOTE Confidence: 0.9023082

00:10:38.390 --> 00:10:39.750 we ask questions. This is

NOTE Confidence: 0.9023082

00:10:39.750 --> 00:10:42.415 an inverted inverted classroom. So

NOTE Confidence: 0.9023082

00:10:42.415 --> 00:10:43.375 so the so I I

NOTE Confidence: 0.9023082

00:10:43.375 --> 00:10:44.735 did have a question. One

NOTE Confidence: 0.9023082

00:10:44.815 --> 00:10:45.574 but the first thing is,

NOTE Confidence: 0.9023082

00:10:45.574 --> 00:10:46.514 you know, congratulations

NOTE Confidence: 0.95582086

00:10:46.815 --> 00:10:48.175 to you and, and everyone

NOTE Confidence: 0.95582086

00:10:48.175 --> 00:10:49.315 for, you know, the symposium

NOTE Confidence: 0.9785433

00:10:49.774 --> 00:10:50.975 and for the open science.

NOTE Confidence: 0.9785433

00:10:50.975 --> 00:10:51.694 I think, you know, that

NOTE Confidence: 0.9785433

00:10:51.855 --> 00:10:53.214 that's something that I, I

NOTE Confidence: 0.9785433

00:10:53.214 --> 00:10:54.014 think it's, you know, it's

NOTE Confidence: 0.9785433

00:10:54.014 --> 00:10:55.875 super important for everyone,

NOTE Confidence: 0.99717253

00:10:56.339 --> 00:10:57.540 not just for, you know,

NOTE Confidence: 0.99717253

00:10:57.540 --> 00:10:58.040 academic

NOTE Confidence: 0.9826458

00:10:58.660 --> 00:11:00.100 people, but also for industry

NOTE Confidence: 0.9826458

00:11:00.100 --> 00:11:00.980 and how you know, and

NOTE Confidence: 0.9826458

00:11:00.980 --> 00:11:02.279 for patients as well.

NOTE Confidence: 0.96958435

00:11:02.899 --> 00:11:04.500 Then second, I'm gonna answer

NOTE Confidence: 0.96958435

00:11:04.500 --> 00:11:05.620 the question. And then third,

NOTE Confidence: 0.96958435

00:11:05.620 --> 00:11:06.980 I'm gonna throw a question

NOTE Confidence: 0.96958435

00:11:06.980 --> 00:11:08.019 at at you guys as

NOTE Confidence: 0.96958435

00:11:08.019 --> 00:11:10.019 well. So, from from that,

NOTE Confidence: 0.96958435

00:11:10.019 --> 00:11:11.079 I, you know,

NOTE Confidence: 0.95838535

00:11:11.495 --> 00:11:12.934 I think there's definitely and

NOTE Confidence: 0.95838535

00:11:12.934 --> 00:11:14.954 we were discussing earlier today,

NOTE Confidence: 0.89644235

00:11:15.975 --> 00:11:17.654 whether the lysosomes yeah. What's

NOTE Confidence: 0.89644235

00:11:17.654 --> 00:11:18.954 the function of the lysosomes

NOTE Confidence: 0.89644235

00:11:19.014 --> 00:11:20.054 and how do how do

NOTE Confidence: 0.89644235

00:11:20.054 --> 00:11:20.795 they impact,

NOTE Confidence: 0.90087914

00:11:21.175 --> 00:11:22.695 disease, not only risk, but

NOTE Confidence: 0.90087914

00:11:22.695 --> 00:11:24.235 also progression of the disease

NOTE Confidence: 0.90087914

00:11:24.375 --> 00:11:25.495 in general and how we

NOTE Confidence: 0.90087914

00:11:25.495 --> 00:11:26.160 target it.

NOTE Confidence: 0.97591037

00:11:26.720 --> 00:11:27.600 I I don't I don't

NOTE Confidence: 0.97591037

00:11:27.600 --> 00:11:29.279 think we're just scratching the

NOTE Confidence: 0.97591037

00:11:29.279 --> 00:11:30.559 surface. And if we think

NOTE Confidence: 0.97591037

00:11:30.559 --> 00:11:31.759 about even the trials that

NOTE Confidence: 0.97591037

00:11:31.759 --> 00:11:33.679 are go ongoing, that are

NOTE Confidence: 0.97591037

00:11:33.679 --> 00:11:36.319 related to lysosomal functions, whether

NOTE Confidence: 0.97591037

00:11:36.319 --> 00:11:37.120 it was, you know, our

NOTE Confidence: 0.97591037

00:11:37.120 --> 00:11:38.339 Vangustat trial,

NOTE Confidence: 0.6709728

00:11:38.725 --> 00:11:40.085 the trials from our lecture

NOTE Confidence: 0.6709728

00:11:40.085 --> 00:11:40.745 on programmiling

NOTE Confidence: 0.91695905

00:11:41.125 --> 00:11:42.325 or the try or, you

NOTE Confidence: 0.91695905

00:11:42.325 --> 00:11:44.325 know, programmiling or the Lark

NOTE Confidence: 0.91695905

00:11:44.325 --> 00:11:46.005 two, etcetera. I think there's

NOTE Confidence: 0.91695905

00:11:46.005 --> 00:11:46.965 a lot that we need

NOTE Confidence: 0.91695905

00:11:46.965 --> 00:11:48.085 to learn about how to,

NOTE Confidence: 0.91695905

00:11:48.085 --> 00:11:48.665 you know,

NOTE Confidence: 0.98006827

00:11:48.965 --> 00:11:50.505 target this from a progression

NOTE Confidence: 0.98006827

00:11:50.565 --> 00:11:51.385 point of view.

NOTE Confidence: 0.9015698

00:11:51.759 --> 00:11:53.600 It's super complicated. Even for

NOTE Confidence: 0.9015698

00:11:53.600 --> 00:11:55.040 Garcetti's disease, that it's a

NOTE Confidence: 0.9015698

00:11:55.040 --> 00:11:55.940 single monogenic

NOTE Confidence: 0.9167847

00:11:56.800 --> 00:11:58.000 disorder, we can see that

NOTE Confidence: 0.9167847

00:11:58.000 --> 00:11:59.300 there is, more complications

NOTE Confidence: 0.90612453

00:11:59.679 --> 00:12:01.440 than just the the enzyme

NOTE Confidence: 0.90612453

00:12:01.440 --> 00:12:02.420 replacement therapy.

NOTE Confidence: 0.97723514

00:12:03.600 --> 00:12:04.720 And then how do this

NOTE Confidence: 0.97723514

00:12:04.720 --> 00:12:05.839 play out in a in

NOTE Confidence: 0.97723514

00:12:05.839 --> 00:12:06.500 a sequential

NOTE Confidence: 0.9483381

00:12:07.125 --> 00:12:08.645 manner? You know, whether if

NOTE Confidence: 0.9483381

00:12:08.645 --> 00:12:10.085 we fix the pro granular

NOTE Confidence: 0.9483381

00:12:10.085 --> 00:12:11.365 defect, what are we gonna

NOTE Confidence: 0.9483381

00:12:11.365 --> 00:12:12.485 do? And this is a

NOTE Confidence: 0.9483381

00:12:12.485 --> 00:12:14.725 precision medicine approach that your

NOTE Confidence: 0.9483381

00:12:14.804 --> 00:12:16.165 you and many others are,

NOTE Confidence: 0.9483381

00:12:16.245 --> 00:12:17.684 you know, trying to put

NOTE Confidence: 0.9483381

00:12:17.684 --> 00:12:19.365 forward for Parkinson's and other

NOTE Confidence: 0.9483381

00:12:19.365 --> 00:12:19.865 neurodegenerative

NOTE Confidence: 0.9876187

00:12:20.245 --> 00:12:20.745 diseases.

NOTE Confidence: 0.99918664

00:12:21.285 --> 00:12:22.265 So I think we're

NOTE Confidence: 0.9481846

00:12:22.790 --> 00:12:24.629 just scratching the surface. I'm

NOTE Confidence: 0.9481846

00:12:24.629 --> 00:12:25.670 sorry. I don't have a

NOTE Confidence: 0.9481846

00:12:25.670 --> 00:12:27.029 good answer to, say, you

NOTE Confidence: 0.9481846

00:12:27.029 --> 00:12:27.529 know,

NOTE Confidence: 0.93669647

00:12:28.149 --> 00:12:29.269 I I don't think there's

NOTE Confidence: 0.93669647

00:12:29.269 --> 00:12:30.790 one only one enzyme that

NOTE Confidence: 0.93669647

00:12:30.790 --> 00:12:32.250 it you know, it's downstream

NOTE Confidence: 0.93669647

00:12:32.389 --> 00:12:33.509 of the program link or

NOTE Confidence: 0.93669647

00:12:33.509 --> 00:12:34.870 the TMN one that that

NOTE Confidence: 0.93669647

00:12:34.870 --> 00:12:35.765 we can go and say,

NOTE Confidence: 0.93669647

00:12:35.765 --> 00:12:36.684 you know, if we fix

NOTE Confidence: 0.93669647

00:12:36.684 --> 00:12:38.285 that defect, we're gonna fix

NOTE Confidence: 0.93669647

00:12:38.285 --> 00:12:38.945 it all.

NOTE Confidence: 0.9886769

00:12:39.325 --> 00:12:40.765 And that's why the precision

NOTE Confidence: 0.9886769

00:12:40.765 --> 00:12:41.985 medicine is gonna be important.

NOTE Confidence: 0.9824195

00:12:43.325 --> 00:12:44.525 And for the precision, I

NOTE Confidence: 0.9824195

00:12:44.765 --> 00:12:46.525 the way I foresee it,

NOTE Confidence: 0.9824195

00:12:46.525 --> 00:12:47.985 maybe that's more important,

NOTE Confidence: 0.97743416

00:12:48.920 --> 00:12:50.519 is we're gonna have different

NOTE Confidence: 0.97743416

00:12:50.519 --> 00:12:52.620 approaches that will move biomarkers

NOTE Confidence: 0.98420995

00:12:53.160 --> 00:12:54.200 at some point. And, you

NOTE Confidence: 0.98420995

00:12:54.200 --> 00:12:55.880 know, proteomic biomarkers are the

NOTE Confidence: 0.98420995

00:12:55.880 --> 00:12:56.860 ones that are closer

NOTE Confidence: 0.99040484

00:12:57.399 --> 00:12:57.899 today,

NOTE Confidence: 0.9906194

00:12:58.679 --> 00:12:59.980 to in in the clinical

NOTE Confidence: 0.9906194

00:13:00.040 --> 00:13:00.540 applications.

NOTE Confidence: 0.9528268

00:13:01.865 --> 00:13:02.904 And when we see that

NOTE Confidence: 0.9528268

00:13:02.904 --> 00:13:04.504 the biomarkers are moving in

NOTE Confidence: 0.9528268

00:13:04.504 --> 00:13:05.625 the right direction, then those

NOTE Confidence: 0.9528268

00:13:05.625 --> 00:13:06.264 are the patients that are

NOTE Confidence: 0.9528268

00:13:06.264 --> 00:13:07.545 gonna find a benefit, and

NOTE Confidence: 0.9528268

00:13:07.545 --> 00:13:09.084 we're gonna continue with those.

NOTE Confidence: 0.9528268

00:13:09.225 --> 00:13:10.425 And if the biomarkers are

NOTE Confidence: 0.9528268

00:13:10.425 --> 00:13:11.464 not moving, then we're gonna

NOTE Confidence: 0.9528268

00:13:11.545 --> 00:13:12.425 we have to stop the

NOTE Confidence: 0.9528268

00:13:12.425 --> 00:13:12.925 therapy.

NOTE Confidence: 0.9115877

00:13:13.304 --> 00:13:15.004 And that's as, you know,

NOTE Confidence: 0.9094642

00:13:15.740 --> 00:13:17.520 silly or or human intelligence,

NOTE Confidence: 0.9094642

00:13:17.740 --> 00:13:19.120 not AI, but HI

NOTE Confidence: 0.9424267

00:13:19.580 --> 00:13:21.260 as we can be, I

NOTE Confidence: 0.9424267

00:13:21.260 --> 00:13:22.559 think at this point.

NOTE Confidence: 0.9355711

00:13:22.940 --> 00:13:24.940 And then okay. Then I

NOTE Confidence: 0.9355711

00:13:24.940 --> 00:13:26.240 kind of answered the question.

NOTE Confidence: 0.9679787

00:13:27.020 --> 00:13:27.940 And for a quiet guy,

NOTE Confidence: 0.9679787

00:13:27.940 --> 00:13:28.860 I think I talked too

NOTE Confidence: 0.9679787

00:13:28.860 --> 00:13:29.600 much already.

NOTE Confidence: 0.9869388

00:13:30.125 --> 00:13:31.045 And then I'm gonna throw

NOTE Confidence: 0.9869388

00:13:31.045 --> 00:13:32.045 a question at you guys

NOTE Confidence: 0.9869388

00:13:32.045 --> 00:13:33.005 because, you know, we we

NOTE Confidence: 0.9869388

00:13:33.005 --> 00:13:34.445 think about risk factors and

NOTE Confidence: 0.9869388

00:13:34.445 --> 00:13:34.945 project

NOTE Confidence: 0.47971496

00:13:35.404 --> 00:13:36.464 and and,

NOTE Confidence: 0.87493557

00:13:37.245 --> 00:13:38.545 progression of the disease.

NOTE Confidence: 0.9991875

00:13:40.125 --> 00:13:41.325 How can we use the

NOTE Confidence: 0.9991875

00:13:41.325 --> 00:13:43.080 models that you're setting up

NOTE Confidence: 0.9991875

00:13:43.320 --> 00:13:44.620 in order to understand

NOTE Confidence: 0.9439665

00:13:45.000 --> 00:13:46.700 or to to make trials

NOTE Confidence: 0.9997975

00:13:47.160 --> 00:13:47.660 faster

NOTE Confidence: 0.9567545

00:13:48.280 --> 00:13:49.100 and smarter?

NOTE Confidence: 0.9690825

00:13:49.720 --> 00:13:50.840 And is there something that

NOTE Confidence: 0.9690825

00:13:50.840 --> 00:13:51.720 we can you know, if

NOTE Confidence: 0.9690825

00:13:51.720 --> 00:13:53.080 we leverage the models where

NOTE Confidence: 0.9690825

00:13:53.080 --> 00:13:54.390 you see the even

NOTE Confidence: 0.8811939

00:13:55.254 --> 00:13:55.574 project,

NOTE Confidence: 0.9303134

00:13:56.054 --> 00:13:57.415 how the different cell types

NOTE Confidence: 0.9303134

00:13:57.415 --> 00:13:58.795 are being affected,

NOTE Confidence: 0.9567486

00:13:59.574 --> 00:14:00.855 can we learn something about

NOTE Confidence: 0.9567486

00:14:00.855 --> 00:14:02.855 biology using GBA and Lark

NOTE Confidence: 0.9567486

00:14:02.855 --> 00:14:04.475 two as two very simple

NOTE Confidence: 0.9752291

00:14:05.654 --> 00:14:07.574 modifiers for progression of the

NOTE Confidence: 0.9752291

00:14:07.574 --> 00:14:09.100 disease? Both are risk factors,

NOTE Confidence: 0.9752291

00:14:09.100 --> 00:14:10.300 but the progression seems to

NOTE Confidence: 0.9752291

00:14:10.300 --> 00:14:11.420 be very different for those

NOTE Confidence: 0.9752291

00:14:11.420 --> 00:14:12.160 two patients.

NOTE Confidence: 0.9428492

00:14:12.699 --> 00:14:13.339 So I think it's a

NOTE Confidence: 0.9428492

00:14:13.339 --> 00:14:14.300 question for you and for,

NOTE Confidence: 0.9428492

00:14:14.540 --> 00:14:15.679 you know, doctor Dong.

NOTE Confidence: 0.99863756

00:14:16.620 --> 00:14:17.120 Yeah.

NOTE Confidence: 0.9538108

00:14:17.980 --> 00:14:19.019 Yeah. I have a lot

NOTE Confidence: 0.9538108

00:14:19.019 --> 00:14:20.240 to say about it, but,

NOTE Confidence: 0.9212031

00:14:20.855 --> 00:14:22.215 Jason, you might have something

NOTE Confidence: 0.9212031

00:14:22.215 --> 00:14:23.095 to say about this as

NOTE Confidence: 0.9212031

00:14:23.095 --> 00:14:25.335 well. Yeah. This is perhaps

NOTE Confidence: 0.9212031

00:14:25.335 --> 00:14:26.075 not exactly,

NOTE Confidence: 0.91958845

00:14:26.535 --> 00:14:27.015 related,

NOTE Confidence: 0.99121004

00:14:27.575 --> 00:14:28.495 a direct answer, but it

NOTE Confidence: 0.99121004

00:14:28.535 --> 00:14:30.075 it's very related, which is,

NOTE Confidence: 0.99121004

00:14:30.375 --> 00:14:32.375 thinking about you mentioned clinical

NOTE Confidence: 0.99121004

00:14:32.375 --> 00:14:33.575 trials and how we can

NOTE Confidence: 0.99121004

00:14:33.575 --> 00:14:35.335 evaluate whether a drug is

NOTE Confidence: 0.99121004

00:14:35.335 --> 00:14:35.835 working,

NOTE Confidence: 0.9506061

00:14:36.149 --> 00:14:37.610 and and kind of also

NOTE Confidence: 0.9506061

00:14:37.750 --> 00:14:38.149 the,

NOTE Confidence: 0.9832567

00:14:38.949 --> 00:14:40.230 kind of the trajectory of

NOTE Confidence: 0.9832567

00:14:40.230 --> 00:14:41.449 of, development

NOTE Confidence: 0.9690037

00:14:42.069 --> 00:14:43.930 is using these digital biomarkers.

NOTE Confidence: 0.9690037

00:14:44.069 --> 00:14:45.430 So let's just say we

NOTE Confidence: 0.9690037

00:14:45.430 --> 00:14:47.190 have a sensor, watch, whatever

NOTE Confidence: 0.9690037

00:14:47.190 --> 00:14:48.385 it may be, and we

NOTE Confidence: 0.9690037

00:14:48.385 --> 00:14:49.825 can build an AI model

NOTE Confidence: 0.9690037

00:14:49.825 --> 00:14:51.765 that really represents the severity

NOTE Confidence: 0.9690037

00:14:51.904 --> 00:14:52.945 of the progression of an

NOTE Confidence: 0.9690037

00:14:52.945 --> 00:14:53.445 individual.

NOTE Confidence: 0.9817441

00:14:54.545 --> 00:14:56.065 In the context of a

NOTE Confidence: 0.9817441

00:14:56.065 --> 00:14:58.385 a clinical drug trial, instead

NOTE Confidence: 0.9817441

00:14:58.385 --> 00:15:00.644 of waiting perhaps ten weeks

NOTE Confidence: 0.9817441

00:15:00.865 --> 00:15:01.904 for kind of a clinical

NOTE Confidence: 0.9817441

00:15:01.904 --> 00:15:03.870 endpoint to be measured, now

NOTE Confidence: 0.9817441

00:15:04.090 --> 00:15:05.210 you you have a live

NOTE Confidence: 0.9817441

00:15:05.210 --> 00:15:07.290 marker at every given hour

NOTE Confidence: 0.9817441

00:15:07.290 --> 00:15:08.570 how someone is changing and

NOTE Confidence: 0.9817441

00:15:08.570 --> 00:15:10.410 responding to that, to that

NOTE Confidence: 0.9817441

00:15:10.410 --> 00:15:11.290 drug. And so I think

NOTE Confidence: 0.9817441

00:15:11.290 --> 00:15:13.050 that's one of the ways

NOTE Confidence: 0.9817441

00:15:13.050 --> 00:15:14.410 that something like a digital

NOTE Confidence: 0.9817441

00:15:14.410 --> 00:15:15.770 marker, whether it be with

NOTE Confidence: 0.9817441

00:15:15.770 --> 00:15:17.790 wearables or other sensor technology,

NOTE Confidence: 0.9817441

00:15:17.850 --> 00:15:19.185 can can aid that.

NOTE Confidence: 0.99252295

00:15:20.145 --> 00:15:22.065 And and so, in in

NOTE Confidence: 0.99252295

00:15:22.065 --> 00:15:23.365 the drug development,

NOTE Confidence: 0.9280619

00:15:24.385 --> 00:15:26.225 platform that we're building up

NOTE Confidence: 0.9280619

00:15:26.225 --> 00:15:27.425 at the Adam Center, we

NOTE Confidence: 0.9280619

00:15:27.425 --> 00:15:28.865 are we are trying to

NOTE Confidence: 0.9280619

00:15:28.865 --> 00:15:30.705 do, two things. Number one,

NOTE Confidence: 0.9280619

00:15:30.705 --> 00:15:31.200 to do,

NOTE Confidence: 0.9362885

00:15:32.240 --> 00:15:33.760 clinical trials in a dish

NOTE Confidence: 0.9362885

00:15:33.760 --> 00:15:35.300 using personal personal

NOTE Confidence: 0.9736223

00:15:35.600 --> 00:15:37.200 stem cells from from patient

NOTE Confidence: 0.9736223

00:15:37.360 --> 00:15:38.980 from our Yale Harvard biomarker

NOTE Confidence: 0.9736223

00:15:39.040 --> 00:15:39.540 study

NOTE Confidence: 0.95931196

00:15:39.920 --> 00:15:40.420 to,

NOTE Confidence: 0.9274288

00:15:41.200 --> 00:15:42.900 sort of use this patient

NOTE Confidence: 0.9274288

00:15:42.960 --> 00:15:45.240 avatars, not just one, but

NOTE Confidence: 0.9274288

00:15:45.240 --> 00:15:47.675 a a a cohort of

NOTE Confidence: 0.9274288

00:15:47.735 --> 00:15:50.135 patient stem cells with with

NOTE Confidence: 0.9274288

00:15:50.135 --> 00:15:51.255 with, you know, for example,

NOTE Confidence: 0.9274288

00:15:51.255 --> 00:15:52.935 the PM twenty d one,

NOTE Confidence: 0.9996408

00:15:53.334 --> 00:15:53.834 variant

NOTE Confidence: 0.97437286

00:15:54.455 --> 00:15:54.855 to,

NOTE Confidence: 0.90806335

00:15:55.495 --> 00:15:57.175 to as an initial test

NOTE Confidence: 0.90806335

00:15:57.175 --> 00:15:57.834 for drugs.

NOTE Confidence: 0.9869809

00:15:58.214 --> 00:15:59.515 And then if they respond,

NOTE Confidence: 0.9869809

00:15:59.654 --> 00:16:02.100 recontact the patients and stratify

NOTE Confidence: 0.9348775

00:16:02.480 --> 00:16:04.260 clinical trials by targeting,

NOTE Confidence: 0.9633672

00:16:05.040 --> 00:16:06.740 carriers with with the genetic

NOTE Confidence: 0.9633672

00:16:06.800 --> 00:16:07.300 variants.

NOTE Confidence: 0.91517377

00:16:07.920 --> 00:16:08.420 And,

NOTE Confidence: 0.9316087

00:16:09.680 --> 00:16:10.160 we,

NOTE Confidence: 0.9400828

00:16:10.880 --> 00:16:11.780 also have,

NOTE Confidence: 0.98514456

00:16:12.960 --> 00:16:13.460 biofluids

NOTE Confidence: 0.97496825

00:16:13.865 --> 00:16:15.065 for for all of these

NOTE Confidence: 0.97496825

00:16:15.065 --> 00:16:15.565 patients,

NOTE Confidence: 0.8699035

00:16:16.105 --> 00:16:17.805 blood and impart CSF.

NOTE Confidence: 0.9615262

00:16:18.425 --> 00:16:19.944 And so then we, you

NOTE Confidence: 0.9615262

00:16:19.944 --> 00:16:21.384 know, go to freezers to

NOTE Confidence: 0.9615262

00:16:21.384 --> 00:16:22.925 develop tailored biomarkers.

NOTE Confidence: 0.97860444

00:16:23.384 --> 00:16:25.165 So that that's that's really

NOTE Confidence: 0.97860444

00:16:25.305 --> 00:16:27.084 sort of the in,

NOTE Confidence: 0.9985726

00:16:27.860 --> 00:16:28.760 the drug development

NOTE Confidence: 0.9391714

00:16:29.060 --> 00:16:30.440 strategy. And then we're

NOTE Confidence: 0.96940845

00:16:30.820 --> 00:16:32.900 planning to and hoping to

NOTE Confidence: 0.96940845

00:16:32.900 --> 00:16:34.900 work with Luke Lee, who

NOTE Confidence: 0.96940845

00:16:34.900 --> 00:16:36.520 will tell more about his,

NOTE Confidence: 0.9659445

00:16:37.380 --> 00:16:39.140 Parkinson's brain on a chip

NOTE Confidence: 0.9659445

00:16:39.140 --> 00:16:41.220 model for for for for

NOTE Confidence: 0.9659445

00:16:41.220 --> 00:16:42.280 for drug development.

NOTE Confidence: 0.9825941

00:16:43.625 --> 00:16:44.985 And and so so I

NOTE Confidence: 0.9825941

00:16:44.985 --> 00:16:46.345 think both at the level

NOTE Confidence: 0.9825941

00:16:46.345 --> 00:16:47.245 of preclinical

NOTE Confidence: 0.981529

00:16:47.785 --> 00:16:48.985 trials and then,

NOTE Confidence: 0.98997635

00:16:49.464 --> 00:16:51.545 clinical stratification based on on

NOTE Confidence: 0.98997635

00:16:51.545 --> 00:16:52.045 genetics,

NOTE Confidence: 0.993267

00:16:52.825 --> 00:16:54.345 I think we can make

NOTE Confidence: 0.993267

00:16:54.345 --> 00:16:55.165 make a headway.

NOTE Confidence: 0.9706834

00:16:56.510 --> 00:16:57.710 So I would like to

NOTE Confidence: 0.9706834

00:16:57.710 --> 00:16:59.390 thank everyone. Jesse, is your

NOTE Confidence: 0.9706834

00:16:59.390 --> 00:17:00.610 question a short one?

NOTE Confidence: 0.88263077

00:17:01.710 --> 00:17:03.310 Because we have only this

NOTE Confidence: 0.88263077

00:17:03.310 --> 00:17:04.750 view between you and the

NOTE Confidence: 0.88263077

00:17:04.750 --> 00:17:06.030 country. I'll I'll I'll try

NOTE Confidence: 0.88263077

00:17:06.030 --> 00:17:08.270 the best short. So, Thomas,

NOTE Confidence: 0.88263077

00:17:08.270 --> 00:17:09.090 really congratulations

NOTE Confidence: 0.9996097

00:17:09.470 --> 00:17:10.369 on this notion

NOTE Confidence: 0.9870862

00:17:10.865 --> 00:17:12.065 of looking at what I've

NOTE Confidence: 0.9870862

00:17:12.065 --> 00:17:13.744 always called the dark matter

NOTE Confidence: 0.9870862

00:17:13.744 --> 00:17:14.484 of the genome.

NOTE Confidence: 0.9558249

00:17:14.865 --> 00:17:16.545 Yeah. Those seventy five hundred

NOTE Confidence: 0.9558249

00:17:16.545 --> 00:17:17.205 and six,

NOTE Confidence: 0.9993175

00:17:20.625 --> 00:17:22.645 genetic elements that may affect

NOTE Confidence: 0.9859269

00:17:23.340 --> 00:17:24.640 disease development progression.

NOTE Confidence: 0.9858862

00:17:25.100 --> 00:17:26.380 But when you my question

NOTE Confidence: 0.9858862

00:17:26.380 --> 00:17:27.919 for you is this. Conceptually,

NOTE Confidence: 0.9858862

00:17:28.059 --> 00:17:29.260 when you target one of

NOTE Confidence: 0.9858862

00:17:29.260 --> 00:17:29.760 those

NOTE Confidence: 0.9889553

00:17:31.100 --> 00:17:32.000 in the dish,

NOTE Confidence: 0.99928993

00:17:33.179 --> 00:17:34.240 how do you account

NOTE Confidence: 0.9982554

00:17:34.619 --> 00:17:36.539 for what's going on with

NOTE Confidence: 0.9982554

00:17:36.539 --> 00:17:37.600 the other seven

NOTE Confidence: 0.9999714

00:17:38.205 --> 00:17:38.705 thousand

NOTE Confidence: 0.9867436

00:17:39.565 --> 00:17:40.845 five hundred and five or

NOTE Confidence: 0.9867436

00:17:40.845 --> 00:17:42.365 a significant fraction of those

NOTE Confidence: 0.9867436

00:17:42.365 --> 00:17:43.744 that might also be

NOTE Confidence: 0.92949843

00:17:44.205 --> 00:17:46.284 affecting disease progression and the

NOTE Confidence: 0.92949843

00:17:46.284 --> 00:17:46.784 variability,

NOTE Confidence: 0.8404251

00:17:47.484 --> 00:17:48.625 the inter patient

NOTE Confidence: 0.99944204

00:17:49.325 --> 00:17:49.825 variability

NOTE Confidence: 0.98169434

00:17:50.445 --> 00:17:51.904 that those small differences

NOTE Confidence: 0.97499275

00:17:52.525 --> 00:17:53.265 might introduce.

NOTE Confidence: 0.9845761

00:17:54.179 --> 00:17:55.859 Right. It it sort of,

NOTE Confidence: 0.9845761

00:17:56.179 --> 00:17:57.480 looks like, you know,

NOTE Confidence: 0.9997671

00:17:58.659 --> 00:17:59.159 impossible

NOTE Confidence: 0.96957713

00:17:59.619 --> 00:18:00.500 sort of at the at

NOTE Confidence: 0.96957713

00:18:00.500 --> 00:18:01.779 the macro level. But, actually,

NOTE Confidence: 0.96957713

00:18:01.779 --> 00:18:02.840 if you dig into,

NOTE Confidence: 0.9983235

00:18:04.100 --> 00:18:04.600 specific

NOTE Confidence: 0.98178726

00:18:05.859 --> 00:18:08.019 variants and specific target genes

NOTE Confidence: 0.98178726

00:18:08.019 --> 00:18:10.025 and target pathways, it becomes

NOTE Confidence: 0.98178726

00:18:10.025 --> 00:18:11.325 all much more clear.

NOTE Confidence: 0.93169785

00:18:11.865 --> 00:18:13.304 For example, one of the

NOTE Confidence: 0.93169785

00:18:13.304 --> 00:18:15.544 GWAS functional GWAS target genes

NOTE Confidence: 0.93169785

00:18:15.544 --> 00:18:17.544 we found is SCARP two,

NOTE Confidence: 0.93169785

00:18:17.544 --> 00:18:18.365 which is,

NOTE Confidence: 0.840381

00:18:18.984 --> 00:18:20.525 produces the lam protein,

NOTE Confidence: 0.99190485

00:18:21.304 --> 00:18:22.605 which is the transporter

NOTE Confidence: 0.91664517

00:18:23.065 --> 00:18:25.609 for GKs, GBA from the

NOTE Confidence: 0.91664517

00:18:25.609 --> 00:18:26.830 ER to the lysosome.

NOTE Confidence: 0.92585677

00:18:27.450 --> 00:18:28.590 And so, clearly,

NOTE Confidence: 0.9726261

00:18:30.650 --> 00:18:32.750 if you target this pathway,

NOTE Confidence: 0.9890934

00:18:33.210 --> 00:18:34.970 that should work for the

NOTE Confidence: 0.9890934

00:18:34.970 --> 00:18:36.330 ten percent of patients that

NOTE Confidence: 0.9890934

00:18:36.330 --> 00:18:37.710 carry the GBA mutation

NOTE Confidence: 0.8998663

00:18:38.205 --> 00:18:39.645 and and, you know, the

NOTE Confidence: 0.8998663

00:18:39.804 --> 00:18:41.725 whatever percentage of patient carrying

NOTE Confidence: 0.8998663

00:18:41.725 --> 00:18:43.184 the SCARB two mutation.

NOTE Confidence: 0.9863078

00:18:43.725 --> 00:18:45.085 So I think so that's

NOTE Confidence: 0.9863078

00:18:45.085 --> 00:18:46.304 that's, I think, one,

NOTE Confidence: 0.99967873

00:18:46.924 --> 00:18:48.385 way to make this work.

NOTE Confidence: 0.93448865

00:18:49.005 --> 00:18:50.945 The other is we are

NOTE Confidence: 0.9527545

00:18:51.270 --> 00:18:52.710 today, you know, we focused

NOTE Confidence: 0.9527545

00:18:52.710 --> 00:18:55.210 on sort of one variant,

NOTE Confidence: 0.99876696

00:18:55.590 --> 00:18:56.890 one well,

NOTE Confidence: 0.9814403

00:18:57.510 --> 00:18:58.010 pleiotropic

NOTE Confidence: 0.9590353

00:18:58.390 --> 00:18:59.290 target genes.

NOTE Confidence: 0.9855492

00:18:59.830 --> 00:19:01.430 But, actually, you know, the

NOTE Confidence: 0.9855492

00:19:01.430 --> 00:19:03.350 big vision is really to

NOTE Confidence: 0.9855492

00:19:03.350 --> 00:19:05.265 be able to to input

NOTE Confidence: 0.9855492

00:19:05.345 --> 00:19:06.305 to look at the whole

NOTE Confidence: 0.9855492

00:19:06.305 --> 00:19:06.805 genome,

NOTE Confidence: 0.9304562

00:19:07.505 --> 00:19:08.625 look at all the risk

NOTE Confidence: 0.9304562

00:19:08.625 --> 00:19:09.125 variants

NOTE Confidence: 0.94343185

00:19:09.665 --> 00:19:11.265 a person has that might

NOTE Confidence: 0.94343185

00:19:11.265 --> 00:19:12.725 be Parkinson's variants,

NOTE Confidence: 0.91751397

00:19:13.185 --> 00:19:14.865 might be some Alzheimer's variants.

NOTE Confidence: 0.91751397

00:19:14.865 --> 00:19:15.985 Right? And use it,

NOTE Confidence: 0.9306095

00:19:17.025 --> 00:19:18.165 use this polygenic

NOTE Confidence: 0.97207457

00:19:18.945 --> 00:19:19.445 input

NOTE Confidence: 0.9988329

00:19:19.905 --> 00:19:21.365 to to identify

NOTE Confidence: 0.9975002

00:19:21.825 --> 00:19:22.565 the polygenic,

NOTE Confidence: 0.9699407

00:19:23.505 --> 00:19:25.505 RNA consequences and and and

NOTE Confidence: 0.9699407

00:19:25.505 --> 00:19:26.245 treat them.