WEBVTT

NOTE duration: ”01:05:51.120”

NOTE Confidence: 0.9491072

00:00:00.160 --> 00:00:01.360 And our leadership of our

NOTE Confidence: 0.9491072

00:00:01.360 --> 00:00:02.980 of our CME series for

NOTE Confidence: 0.9491072

00:00:03.199 --> 00:00:03.699 rebranding

NOTE Confidence: 0.87646586

00:00:04.000 --> 00:00:05.680 us and moving us to

NOTE Confidence: 0.87646586

00:00:05.680 --> 00:00:06.500 this date.

NOTE Confidence: 0.98256636

00:00:07.200 --> 00:00:08.020 Last week's

NOTE Confidence: 0.77230656

00:00:08.639 --> 00:00:09.780 introductory session

NOTE Confidence: 0.8992631

00:00:10.080 --> 00:00:11.219 was really wonderful.

NOTE Confidence: 0.9926584

00:00:11.679 --> 00:00:12.400 And the fact that we

NOTE Confidence: 0.9926584

00:00:12.400 --> 00:00:13.280 were able to,

NOTE Confidence: 0.8870735

00:00:14.160 --> 00:00:15.735 kind of, share new ideas

NOTE Confidence: 0.8870735

00:00:15.735 --> 00:00:16.695 of how to continue to

NOTE Confidence: 0.8870735

00:00:16.695 --> 00:00:18.215 build on on this long

NOTE Confidence: 0.8870735

00:00:18.215 --> 00:00:20.134 tradition path of removing to

NOTE Confidence: 0.8870735

00:00:20.134 --> 00:00:21.735 this time and and and

NOTE Confidence: 0.8870735

00:00:21.735 --> 00:00:22.634 day of the week.

NOTE Confidence: 0.95626694

00:00:22.935 --> 00:00:25.515 So, moving forward, obviously, Wednesdays

NOTE Confidence: 0.95626694

00:00:25.814 --> 00:00:27.255 at noon will be our

NOTE Confidence: 0.95626694

00:00:27.255 --> 00:00:28.855 time, and and, and and

NOTE Confidence: 0.95626694

00:00:28.855 --> 00:00:29.970 there is a schedule that

NOTE Confidence: 0.95626694

00:00:29.970 --> 00:00:30.869 would incorporate

NOTE Confidence: 0.93212515

00:00:31.330 --> 00:00:32.530 not only a case based

NOTE Confidence: 0.93212515

00:00:32.530 --> 00:00:34.610 clinical conference led by a

NOTE Confidence: 0.93212515

00:00:34.610 --> 00:00:36.290 fellow and a a faculty

NOTE Confidence: 0.93212515

00:00:36.290 --> 00:00:37.809 mentor for this for the

NOTE Confidence: 0.93212515

00:00:37.809 --> 00:00:39.409 section at large, a research

NOTE Confidence: 0.93212515

00:00:39.409 --> 00:00:41.909 forum led, by doctor Bender,

NOTE Confidence: 0.74941146

00:00:42.610 --> 00:00:43.110 and,

NOTE Confidence: 0.9291608

00:00:44.065 --> 00:00:46.245 at least two visiting professors.

NOTE Confidence: 0.9291608

00:00:46.385 --> 00:00:48.085 One ex you know,

NOTE Confidence: 0.8860952

00:00:49.825 --> 00:00:50.865 one we have today that

NOTE Confidence: 0.8860952

00:00:50.865 --> 00:00:52.405 we'll I'll have Tara describe,

NOTE Confidence: 0.8860952

00:00:52.705 --> 00:00:54.165 and introduce in a moment.

NOTE Confidence: 0.9969121

00:00:54.785 --> 00:00:56.545 Before we get started, I

NOTE Confidence: 0.9969121

00:00:56.545 --> 00:00:58.485 just wanna remind folks that

NOTE Confidence: 0.84983444

00:00:58.900 --> 00:01:00.580 our CME process had not

NOTE Confidence: 0.84983444

00:01:00.580 --> 00:01:01.080 changed,

NOTE Confidence: 0.99046785

00:01:01.940 --> 00:01:02.840 so please

NOTE Confidence: 0.9963179

00:01:03.380 --> 00:01:05.620 use these five numbers to

NOTE Confidence: 0.9963179

00:01:05.620 --> 00:01:07.140 sign on for your CME

NOTE Confidence: 0.9963179

00:01:07.140 --> 00:01:08.840 credit. We'll be tracking this,

NOTE Confidence: 0.9853403

00:01:10.100 --> 00:01:11.220 just to give us a

NOTE Confidence: 0.9853403

00:01:11.220 --> 00:01:11.720 sense.

NOTE Confidence: 0.94259536

00:01:12.100 --> 00:01:12.600 And,

NOTE Confidence: 0.7330388

00:01:13.715 --> 00:01:14.215 also,

NOTE Confidence: 0.9939871

00:01:15.475 --> 00:01:15.975 please

NOTE Confidence: 0.7048223

00:01:16.915 --> 00:01:17.415 separately

NOTE Confidence: 0.9097198

00:01:17.955 --> 00:01:19.475 for the for the foreseeable

NOTE Confidence: 0.9097198

00:01:19.475 --> 00:01:21.475 future, sign up with our

NOTE Confidence: 0.9097198

00:01:21.475 --> 00:01:23.634 administrative team up front because

NOTE Confidence: 0.9097198

00:01:23.634 --> 00:01:24.915 as we have members of

NOTE Confidence: 0.9097198

00:01:24.915 --> 00:01:26.549 the community at large, the

NOTE Confidence: 0.9097198

00:01:26.549 --> 00:01:27.590 heart and vascular center as

NOTE Confidence: 0.9097198

00:01:27.590 --> 00:01:28.549 well as the section in

NOTE Confidence: 0.9097198

00:01:28.549 --> 00:01:29.209 the department,

NOTE Confidence: 0.9875816

00:01:29.990 --> 00:01:31.270 we are trying to just,

NOTE Confidence: 0.9491467

00:01:31.750 --> 00:01:32.569 right size

NOTE Confidence: 0.9634268

00:01:33.189 --> 00:01:34.329 the in room,

NOTE Confidence: 0.9556366

00:01:35.110 --> 00:01:36.149 ordering of food and that

NOTE Confidence: 0.9556366

00:01:36.229 --> 00:01:37.509 so there's two separate things.

NOTE Confidence: 0.9556366

00:01:37.509 --> 00:01:39.209 CME activity is electronic,

NOTE Confidence: 0.976954

00:01:39.645 --> 00:01:40.685 but the sign up is

NOTE Confidence: 0.976954

00:01:40.685 --> 00:01:42.284 really to give our team

NOTE Confidence: 0.976954

00:01:42.284 --> 00:01:44.045 some, information around how to

NOTE Confidence: 0.976954

00:01:44.045 --> 00:01:44.545 plan

NOTE Confidence: 0.97678304

00:01:45.005 --> 00:01:46.525 to make sure we're, good

NOTE Confidence: 0.97678304

00:01:46.525 --> 00:01:48.045 stewards of our finances and

NOTE Confidence: 0.97678304

00:01:48.045 --> 00:01:49.104 don't over order,

NOTE Confidence: 0.9792063

00:01:49.884 --> 00:01:50.284 which,

NOTE Confidence: 0.952807

00:01:50.685 --> 00:01:51.965 unfortunately, is a kind of

NOTE Confidence: 0.952807

00:01:51.965 --> 00:01:53.325 a tradition at Yale from

NOTE Confidence: 0.952807

00:01:53.325 --> 00:01:54.225 what I can tell.

NOTE Confidence: 0.95711726

00:01:56.259 --> 00:01:58.020 And then I, before I

NOTE Confidence: 0.95711726

00:01:58.020 --> 00:01:58.520 get,

NOTE Confidence: 0.9300574

00:01:59.299 --> 00:02:00.920 maybe one other quick intro,

NOTE Confidence: 0.9601358

00:02:01.700 --> 00:02:02.420 just wanna,

NOTE Confidence: 0.7593676

00:02:02.899 --> 00:02:03.399 thank,

NOTE Confidence: 0.9991479

00:02:04.500 --> 00:02:06.119 all the members of our

NOTE Confidence: 0.8864957

00:02:07.220 --> 00:02:09.514 section who are viewing this,

NOTE Confidence: 0.98753065

00:02:09.815 --> 00:02:10.395 live, in

NOTE Confidence: 0.9420754

00:02:11.095 --> 00:02:11.595 groups,

NOTE Confidence: 0.8990552

00:02:12.935 --> 00:02:14.535 at so called watch parties.

NOTE Confidence: 0.8990552

00:02:14.535 --> 00:02:15.575 And hopefully, you got your

NOTE Confidence: 0.8990552

00:02:15.575 --> 00:02:17.495 lunch delivered to Greenwich, New

NOTE Confidence: 0.8990552

00:02:17.495 --> 00:02:18.555 London, and Bridgeport,

NOTE Confidence: 0.98532736

00:02:19.014 --> 00:02:20.294 and wherever you are,

NOTE Confidence: 0.9285441

00:02:20.855 --> 00:02:22.055 at the VA. And I

NOTE Confidence: 0.9285441

00:02:22.055 --> 00:02:23.514 think it's a a wonderful

NOTE Confidence: 0.9285441

00:02:23.655 --> 00:02:24.155 new

NOTE Confidence: 0.9782841

00:02:24.550 --> 00:02:25.050 tradition,

NOTE Confidence: 0.93757653

00:02:25.510 --> 00:02:27.030 so that, we all can

NOTE Confidence: 0.93757653

00:02:27.030 --> 00:02:28.230 come together at wherever we

NOTE Confidence: 0.93757653

00:02:28.230 --> 00:02:28.730 are,

NOTE Confidence: 0.9864626

00:02:29.110 --> 00:02:30.069 for this hour,

NOTE Confidence: 0.9358573

00:02:30.870 --> 00:02:31.930 of of fellowship,

NOTE Confidence: 0.9675173

00:02:32.790 --> 00:02:34.250 and, and collaboration.

NOTE Confidence: 0.9783934

00:02:35.110 --> 00:02:35.990 And so with that,

NOTE Confidence: 0.88563013

00:02:36.565 --> 00:02:38.264 I wanted to, surprisingly,

NOTE Confidence: 0.95041955

00:02:39.925 --> 00:02:40.425 introduce,

NOTE Confidence: 0.9511311

00:02:40.725 --> 00:02:42.405 our new chair, Wolfram Gosling,

NOTE Confidence: 0.9511311

00:02:42.405 --> 00:02:43.605 who's here with us. And

NOTE Confidence: 0.9511311

00:02:43.605 --> 00:02:44.805 everyone give me give him

NOTE Confidence: 0.9511311

00:02:44.805 --> 00:02:45.705 a a hand

NOTE Confidence: 0.8170413

00:02:46.084 --> 00:02:46.665 of applause.

NOTE Confidence: 0.77911663

00:02:49.290 --> 00:02:49.790 Wolfram,

NOTE Confidence: 0.9345753

00:02:50.889 --> 00:02:52.010 reached out this morning,

NOTE Confidence: 0.94200623

00:02:52.410 --> 00:02:53.690 to me and and,

NOTE Confidence: 0.94237244

00:02:54.330 --> 00:02:55.530 just alerted me that he

NOTE Confidence: 0.94237244

00:02:55.530 --> 00:02:56.650 used to be his lab,

NOTE Confidence: 0.94237244

00:02:56.970 --> 00:02:58.330 partner across the hall or

NOTE Confidence: 0.94237244

00:02:58.330 --> 00:02:59.370 somewhere, and your labs were

NOTE Confidence: 0.94237244

00:02:59.370 --> 00:03:00.570 near each other. And he

NOTE Confidence: 0.94237244

00:03:00.570 --> 00:03:02.410 was excited, and and, I,

NOTE Confidence: 0.94237244

00:03:02.650 --> 00:03:03.764 was excited he could join

NOTE Confidence: 0.94237244

00:03:03.764 --> 00:03:04.564 us. But he does not

NOTE Confidence: 0.94237244

00:03:04.564 --> 00:03:05.944 wanna take the thunder away

NOTE Confidence: 0.9649709

00:03:06.325 --> 00:03:08.084 from, Raj. And so, we

NOTE Confidence: 0.9649709

00:03:08.084 --> 00:03:09.364 will leave it for another

NOTE Confidence: 0.9649709

00:03:09.364 --> 00:03:10.485 day to have him more

NOTE Confidence: 0.9649709

00:03:10.485 --> 00:03:11.924 formally introduce himself and his

NOTE Confidence: 0.9649709

00:03:11.924 --> 00:03:12.424 goals

NOTE Confidence: 0.95879596

00:03:12.724 --> 00:03:14.165 to the, section at large.

NOTE Confidence: 0.95879596

00:03:14.165 --> 00:03:15.284 And and those of you

NOTE Confidence: 0.95879596

00:03:15.284 --> 00:03:15.944 who were,

NOTE Confidence: 0.9467116

00:03:16.290 --> 00:03:17.810 as I was inspired by

NOTE Confidence: 0.9467116

00:03:17.810 --> 00:03:19.750 his, town hall for departmental

NOTE Confidence: 0.9467116

00:03:19.810 --> 00:03:20.310 faculty,

NOTE Confidence: 0.93572676

00:03:20.930 --> 00:03:22.130 should certainly, if you weren't

NOTE Confidence: 0.93572676

00:03:22.130 --> 00:03:23.169 able to go look at

NOTE Confidence: 0.93572676

00:03:23.169 --> 00:03:25.030 those slides in that presentation,

NOTE Confidence: 0.93572676

00:03:25.169 --> 00:03:26.050 I think, will be very

NOTE Confidence: 0.93572676

00:03:26.050 --> 00:03:26.950 important. So,

NOTE Confidence: 0.90149695

00:03:27.889 --> 00:03:28.915 well, from my hope, I

NOTE Confidence: 0.90149695

00:03:28.915 --> 00:03:29.794 I didn't make put you

NOTE Confidence: 0.90149695

00:03:29.794 --> 00:03:30.675 too much on the spot,

NOTE Confidence: 0.90149695

00:03:30.675 --> 00:03:31.175 but,

NOTE Confidence: 0.9707525

00:03:31.635 --> 00:03:32.995 so, again, here's the CME

NOTE Confidence: 0.9707525

00:03:32.995 --> 00:03:34.435 activities. This is what we

NOTE Confidence: 0.9707525

00:03:34.435 --> 00:03:35.395 have coming up in the

NOTE Confidence: 0.9707525

00:03:35.395 --> 00:03:36.135 next month.

NOTE Confidence: 0.9706339

00:03:36.915 --> 00:03:38.135 Critical care conference,

NOTE Confidence: 0.9638893

00:03:39.075 --> 00:03:39.795 on the first,

NOTE Confidence: 0.93013066

00:03:41.860 --> 00:03:42.739 and then we have the

NOTE Confidence: 0.93013066

00:03:42.819 --> 00:03:44.099 we have a holiday, a

NOTE Confidence: 0.93013066

00:03:44.099 --> 00:03:45.379 Jewish holiday in the middle,

NOTE Confidence: 0.93013066

00:03:45.540 --> 00:03:47.160 there before our next one.

NOTE Confidence: 0.93013066

00:03:47.300 --> 00:03:48.180 And then Raj,

NOTE Confidence: 0.52907497

00:03:48.500 --> 00:03:50.040 Rajesh Vran Vranasen

NOTE Confidence: 0.96109736

00:03:50.500 --> 00:03:51.640 from, NYU,

NOTE Confidence: 0.95346177

00:03:52.260 --> 00:03:53.620 an imaging case conference, and

NOTE Confidence: 0.95346177

00:03:53.620 --> 00:03:54.705 then Mark Peltier, our new

NOTE Confidence: 0.95346177

00:03:54.705 --> 00:03:55.745 chief of cardiac surgery, is

NOTE Confidence: 0.95346177

00:03:55.745 --> 00:03:57.045 gonna give us grand rounds,

NOTE Confidence: 0.96292514

00:03:57.505 --> 00:03:58.305 towards the end of the

NOTE Confidence: 0.96292514

00:03:58.305 --> 00:03:58.805 month.

NOTE Confidence: 0.97525823

00:03:59.825 --> 00:04:01.105 We also just wanna make

NOTE Confidence: 0.97525823

00:04:01.105 --> 00:04:03.285 a quick announcement for our

NOTE Confidence: 0.97525823

00:04:03.345 --> 00:04:03.845 faculty.

NOTE Confidence: 0.99706936

00:04:04.785 --> 00:04:05.525 We have

NOTE Confidence: 0.9819759

00:04:07.150 --> 00:04:08.750 historically, had our faculty meetings

NOTE Confidence: 0.9819759

00:04:08.750 --> 00:04:10.210 at five o'clock on Wednesdays,

NOTE Confidence: 0.98024607

00:04:10.670 --> 00:04:12.130 which we will have today.

NOTE Confidence: 0.98024607

00:04:12.270 --> 00:04:14.110 Larry Young is on deck

NOTE Confidence: 0.98024607

00:04:14.110 --> 00:04:14.910 to give us a bit

NOTE Confidence: 0.98024607

00:04:14.910 --> 00:04:15.950 of a presentation. It'll be

NOTE Confidence: 0.98024607

00:04:15.950 --> 00:04:17.470 a short fact meeting, but

NOTE Confidence: 0.98024607

00:04:17.470 --> 00:04:18.589 we are going to move

NOTE Confidence: 0.98024607

00:04:18.589 --> 00:04:19.089 those,

NOTE Confidence: 0.94388145

00:04:19.945 --> 00:04:21.305 from here on end to

NOTE Confidence: 0.94388145

00:04:21.305 --> 00:04:22.585 a different day as we

NOTE Confidence: 0.94388145

00:04:22.585 --> 00:04:23.544 move their grand rounds so

NOTE Confidence: 0.94388145

00:04:23.544 --> 00:04:24.525 that there's not

NOTE Confidence: 0.9796287

00:04:24.985 --> 00:04:25.645 too much,

NOTE Confidence: 0.78696096

00:04:26.505 --> 00:04:27.005 time,

NOTE Confidence: 0.7540771

00:04:27.785 --> 00:04:28.525 in conferences,

NOTE Confidence: 0.99890506

00:04:28.904 --> 00:04:30.205 for people to attend.

NOTE Confidence: 0.8101813

00:04:30.664 --> 00:04:31.705 Is there a disclosure to

NOTE Confidence: 0.8101813

00:04:31.705 --> 00:04:32.205 accreditation?

NOTE Confidence: 0.8971821

00:04:32.940 --> 00:04:34.940 And, and, here are our

NOTE Confidence: 0.8971821

00:04:34.940 --> 00:04:36.060 leaders. And if he's that,

NOTE Confidence: 0.8971821

00:04:36.060 --> 00:04:36.960 I'd like to,

NOTE Confidence: 0.99149597

00:04:37.340 --> 00:04:37.840 introduce,

NOTE Confidence: 0.86253744

00:04:38.540 --> 00:04:39.820 Tara Kumar to tell us

NOTE Confidence: 0.86253744

00:04:39.820 --> 00:04:40.800 a little bit about,

NOTE Confidence: 0.93595433

00:04:41.740 --> 00:04:43.340 doctor Gupta and introduce,

NOTE Confidence: 0.9222641

00:04:43.740 --> 00:04:44.480 our speaker.

NOTE Confidence: 0.9434859

00:04:44.860 --> 00:04:46.240 Thanks. Thanks, sir.

NOTE Confidence: 0.98793817

00:04:50.154 --> 00:04:51.775 Good afternoon, everyone. Welcome,

NOTE Confidence: 0.9373086

00:04:52.235 --> 00:04:53.755 back to the academic year,

NOTE Confidence: 0.9373086

00:04:53.755 --> 00:04:54.255 and

NOTE Confidence: 0.97850466

00:04:54.955 --> 00:04:57.595 everyone looks, completely refreshed and

NOTE Confidence: 0.97850466

00:04:57.595 --> 00:04:58.875 good to be back. As

NOTE Confidence: 0.97850466

00:04:58.875 --> 00:04:59.935 someone who

NOTE Confidence: 0.9027694

00:05:00.400 --> 00:05:02.080 ran Grand Rounds sometime back,

NOTE Confidence: 0.9027694

00:05:02.080 --> 00:05:03.460 this is an incredible

NOTE Confidence: 0.96530586

00:05:04.000 --> 00:05:05.599 improvement, and it's so happy

NOTE Confidence: 0.96530586

00:05:05.599 --> 00:05:06.639 to see how all this

NOTE Confidence: 0.96530586

00:05:06.639 --> 00:05:08.000 is going. I do wanna

NOTE Confidence: 0.96530586

00:05:08.000 --> 00:05:09.120 give a special shout out

NOTE Confidence: 0.96530586

00:05:09.120 --> 00:05:11.039 to Joanne who just did

NOTE Confidence: 0.96530586

00:05:11.039 --> 00:05:12.339 an incredible job,

NOTE Confidence: 0.9698287

00:05:12.800 --> 00:05:13.839 with this visit. So thank

NOTE Confidence: 0.9698287

00:05:13.839 --> 00:05:14.960 you and, obviously, the rest

NOTE Confidence: 0.9698287

00:05:14.960 --> 00:05:16.180 of the team as well.

NOTE Confidence: 0.97401315

00:05:17.255 --> 00:05:18.375 So that it's a true

NOTE Confidence: 0.97401315

00:05:18.375 --> 00:05:20.375 honor and privilege to introduce

NOTE Confidence: 0.97401315

00:05:20.375 --> 00:05:22.315 my my friend, Raj Gupta,

NOTE Confidence: 0.9869064

00:05:22.775 --> 00:05:24.294 who's an associate professor of

NOTE Confidence: 0.9869064

00:05:24.294 --> 00:05:26.055 medicine at Harvard Medical School

NOTE Confidence: 0.9869064

00:05:26.055 --> 00:05:27.495 and a physician scientist at

NOTE Confidence: 0.9869064

00:05:27.495 --> 00:05:29.175 the Brigham and Women's Hospital,

NOTE Confidence: 0.9869064

00:05:29.175 --> 00:05:29.675 which

NOTE Confidence: 0.92399967

00:05:30.055 --> 00:05:31.915 is now mass general Brigham,

NOTE Confidence: 0.92399967

00:05:31.975 --> 00:05:33.229 of course.

NOTE Confidence: 0.99717116

00:05:33.710 --> 00:05:34.210 Raj,

NOTE Confidence: 0.97879684

00:05:34.830 --> 00:05:36.370 born and raised in Michigan,

NOTE Confidence: 0.95889455

00:05:36.990 --> 00:05:37.630 went to,

NOTE Confidence: 0.8841191

00:05:38.190 --> 00:05:39.490 Michigan for undergrad.

NOTE Confidence: 0.9756907

00:05:40.110 --> 00:05:41.550 He reminds us often that

NOTE Confidence: 0.9756907

00:05:41.550 --> 00:05:43.150 we're at the Michigan of

NOTE Confidence: 0.9756907

00:05:43.150 --> 00:05:44.865 the East here at Yale.

NOTE Confidence: 0.89704096

00:05:45.585 --> 00:05:47.025 He went to Penn for,

NOTE Confidence: 0.9291608

00:05:48.145 --> 00:05:49.925 for medical school and then

NOTE Confidence: 0.9291608

00:05:49.985 --> 00:05:52.145 Mass General for for residency

NOTE Confidence: 0.9291608

00:05:52.145 --> 00:05:53.525 and then Brigham for,

NOTE Confidence: 0.93081665

00:05:54.305 --> 00:05:55.745 for fellowship, and he's been

NOTE Confidence: 0.93081665

00:05:55.745 --> 00:05:57.285 sent there since then.

NOTE Confidence: 0.9567962

00:05:58.560 --> 00:06:00.080 Raj has devoted his career

NOTE Confidence: 0.9567962

00:06:00.080 --> 00:06:01.600 to understanding the genetic basis

NOTE Confidence: 0.9567962

00:06:01.600 --> 00:06:02.820 of vascular disease.

NOTE Confidence: 0.9917174

00:06:03.279 --> 00:06:05.120 He pioneered, he's pioneered single

NOTE Confidence: 0.9917174

00:06:05.120 --> 00:06:06.640 cell and CRISPR approaches that

NOTE Confidence: 0.9917174

00:06:06.640 --> 00:06:09.060 have fundamentally reshaped our understanding

NOTE Confidence: 0.99990577

00:06:09.600 --> 00:06:10.339 of cardiovascular

NOTE Confidence: 0.9998746

00:06:10.640 --> 00:06:11.140 biology.

NOTE Confidence: 0.93745905

00:06:11.654 --> 00:06:13.095 His work is, many of

NOTE Confidence: 0.93745905

00:06:13.095 --> 00:06:14.855 you know has been, published

NOTE Confidence: 0.93745905

00:06:14.855 --> 00:06:16.555 in the highest impact journals

NOTE Confidence: 0.9664642

00:06:17.015 --> 00:06:19.095 supported by multiple NIH grants,

NOTE Confidence: 0.9664642

00:06:19.095 --> 00:06:20.535 and his lab is already

NOTE Confidence: 0.9664642

00:06:20.535 --> 00:06:21.035 training

NOTE Confidence: 0.9882523

00:06:21.415 --> 00:06:23.335 the next generation of, of

NOTE Confidence: 0.9882523

00:06:23.335 --> 00:06:24.395 physician scientists.

NOTE Confidence: 0.96006185

00:06:25.339 --> 00:06:26.699 On a personal note, we've

NOTE Confidence: 0.96006185

00:06:26.699 --> 00:06:26.860 known,

NOTE Confidence: 0.9628523

00:06:27.580 --> 00:06:28.620 many of us have known

NOTE Confidence: 0.9628523

00:06:28.620 --> 00:06:30.460 Raj, since our days in

NOTE Confidence: 0.9628523

00:06:30.460 --> 00:06:32.300 in Boston. And even then,

NOTE Confidence: 0.9628523

00:06:32.300 --> 00:06:33.500 it was clear that he

NOTE Confidence: 0.9628523

00:06:33.500 --> 00:06:35.440 was single mindedly driven,

NOTE Confidence: 0.98562557

00:06:36.139 --> 00:06:37.520 by the joy of discovery.

NOTE Confidence: 0.96507716

00:06:38.095 --> 00:06:39.855 And since then and back

NOTE Confidence: 0.96507716

00:06:39.855 --> 00:06:40.755 then as well,

NOTE Confidence: 0.9914694

00:06:41.775 --> 00:06:42.815 chose to live a near

NOTE Confidence: 0.9914694

00:06:42.815 --> 00:06:43.955 monastic existence,

NOTE Confidence: 0.99881506

00:06:44.654 --> 00:06:46.115 in the pursuit of science.

NOTE Confidence: 0.9774213

00:06:47.214 --> 00:06:48.575 So none of us were,

NOTE Confidence: 0.9774213

00:06:48.815 --> 00:06:51.135 surprised when he's, emerging as

NOTE Confidence: 0.9774213

00:06:51.135 --> 00:06:52.115 a leader in cardiovascular

NOTE Confidence: 0.99670637

00:06:53.520 --> 00:06:54.020 medicine.

NOTE Confidence: 0.9023978

00:06:55.039 --> 00:06:56.099 Of course, his scientific,

NOTE Confidence: 0.9780651

00:06:56.479 --> 00:06:58.259 you know, record is is

NOTE Confidence: 0.9780651

00:06:58.400 --> 00:06:59.779 nothing short of extraordinary,

NOTE Confidence: 0.963035

00:07:00.560 --> 00:07:01.599 but we I would be

NOTE Confidence: 0.963035

00:07:01.599 --> 00:07:03.460 remiss if I, didn't mention,

NOTE Confidence: 0.9898025

00:07:03.839 --> 00:07:04.339 that,

NOTE Confidence: 0.99745494

00:07:05.680 --> 00:07:06.885 that on the squash court,

NOTE Confidence: 0.99784875

00:07:07.365 --> 00:07:08.805 the balance of power was

NOTE Confidence: 0.99784875

00:07:08.805 --> 00:07:09.945 very different between,

NOTE Confidence: 0.86604434

00:07:11.125 --> 00:07:13.045 our colleague, Nirard Desai, myself,

NOTE Confidence: 0.86604434

00:07:13.045 --> 00:07:14.185 and and doctor Gupta.

NOTE Confidence: 0.98897463

00:07:14.885 --> 00:07:16.725 And, we beat him really

NOTE Confidence: 0.98897463

00:07:16.725 --> 00:07:17.225 badly,

NOTE Confidence: 0.9959955

00:07:17.685 --> 00:07:18.185 consistently.

NOTE Confidence: 0.9874537

00:07:19.039 --> 00:07:20.479 So no matter how many

NOTE Confidence: 0.9874537

00:07:20.479 --> 00:07:22.020 nature papers he publishes,

NOTE Confidence: 0.99406385

00:07:22.800 --> 00:07:24.080 we will always have the

NOTE Confidence: 0.99406385

00:07:24.080 --> 00:07:24.900 upper hand,

NOTE Confidence: 0.9249668

00:07:25.280 --> 00:07:26.240 when it comes to that

NOTE Confidence: 0.9249668

00:07:26.240 --> 00:07:27.280 time in the squash board.

NOTE Confidence: 0.9249668

00:07:27.280 --> 00:07:28.979 So, Raj, with that,

NOTE Confidence: 0.88166606

00:07:29.360 --> 00:07:29.860 Trent,

NOTE Confidence: 0.9978685

00:07:30.240 --> 00:07:30.740 welcome.

NOTE Confidence: 0.9812295

00:07:35.474 --> 00:07:36.595 Well, thank you for that

NOTE Confidence: 0.9812295

00:07:36.595 --> 00:07:37.895 very unique introduction.

NOTE Confidence: 0.98161846

00:07:38.595 --> 00:07:40.115 A real a true pleasure,

NOTE Confidence: 0.98161846

00:07:40.115 --> 00:07:41.555 I think, to be introduced,

NOTE Confidence: 0.98161846

00:07:41.794 --> 00:07:43.794 by Tarek. I'd say, one

NOTE Confidence: 0.98161846

00:07:43.794 --> 00:07:44.995 of the greatest pleasures and

NOTE Confidence: 0.98161846

00:07:44.995 --> 00:07:46.410 distractions in my life is

NOTE Confidence: 0.98161846

00:07:46.410 --> 00:07:47.130 to be on a text

NOTE Confidence: 0.98161846

00:07:47.130 --> 00:07:48.190 chain with Nihar

NOTE Confidence: 0.93639284

00:07:48.730 --> 00:07:49.950 and Tariq, which,

NOTE Confidence: 0.9491488

00:07:50.490 --> 00:07:51.770 is a a blessing and

NOTE Confidence: 0.9491488

00:07:51.770 --> 00:07:52.810 a curse. But,

NOTE Confidence: 0.9563214

00:07:53.690 --> 00:07:55.130 but one one of the

NOTE Confidence: 0.9563214

00:07:55.130 --> 00:07:56.410 reasons I'm so excited to

NOTE Confidence: 0.9563214

00:07:56.410 --> 00:07:57.850 have been invited, by Tariq,

NOTE Confidence: 0.9563214

00:07:57.850 --> 00:07:58.810 and I'm really grateful to

NOTE Confidence: 0.9563214

00:07:58.810 --> 00:07:59.690 be here, is that, you

NOTE Confidence: 0.9563214

00:07:59.690 --> 00:08:01.210 know, it's it's always great

NOTE Confidence: 0.9563214

00:08:01.210 --> 00:08:02.625 to have friends from your

NOTE Confidence: 0.9563214

00:08:02.625 --> 00:08:03.125 training

NOTE Confidence: 0.9788586

00:08:03.505 --> 00:08:04.705 days who are your biggest

NOTE Confidence: 0.9788586

00:08:04.705 --> 00:08:05.825 cheerleaders and, you know, at

NOTE Confidence: 0.9788586

00:08:05.825 --> 00:08:06.705 this stage of our career

NOTE Confidence: 0.9788586

00:08:06.705 --> 00:08:07.825 to be invited to then

NOTE Confidence: 0.9788586

00:08:07.825 --> 00:08:08.865 present my work in this

NOTE Confidence: 0.9788586

00:08:08.865 --> 00:08:10.465 forum is is is really

NOTE Confidence: 0.9788586

00:08:10.465 --> 00:08:11.425 a highlight. I've been looking

NOTE Confidence: 0.9788586

00:08:11.425 --> 00:08:12.305 forward to this, you know,

NOTE Confidence: 0.9788586

00:08:12.305 --> 00:08:13.365 for about a year,

NOTE Confidence: 0.9962797

00:08:13.985 --> 00:08:15.125 in scheduling it.

NOTE Confidence: 0.97217107

00:08:15.490 --> 00:08:16.449 And, you know, the talk

NOTE Confidence: 0.97217107

00:08:16.449 --> 00:08:17.490 that I wanna give is

NOTE Confidence: 0.97217107

00:08:17.490 --> 00:08:19.169 is about using genetics that

NOTE Confidence: 0.97217107

00:08:19.169 --> 00:08:19.970 we do in a in

NOTE Confidence: 0.97217107

00:08:19.970 --> 00:08:21.569 a my very basic science

NOTE Confidence: 0.97217107

00:08:21.569 --> 00:08:22.930 lab. But I wanna make

NOTE Confidence: 0.97217107

00:08:22.930 --> 00:08:23.729 it, you know, that there's

NOTE Confidence: 0.97217107

00:08:23.729 --> 00:08:25.250 some clinical impact of the

NOTE Confidence: 0.97217107

00:08:25.250 --> 00:08:26.289 work we're doing, and I

NOTE Confidence: 0.97217107

00:08:26.289 --> 00:08:27.729 think that's the challenge that

NOTE Confidence: 0.97217107

00:08:27.729 --> 00:08:28.930 I hope to convince you

NOTE Confidence: 0.97217107

00:08:28.930 --> 00:08:30.050 that, you know, genetics is

NOTE Confidence: 0.97217107

00:08:30.050 --> 00:08:31.145 not just just a an

NOTE Confidence: 0.97217107

00:08:31.145 --> 00:08:32.665 in vitro system that we're

NOTE Confidence: 0.97217107

00:08:32.665 --> 00:08:34.585 we're trying to, tinker with,

NOTE Confidence: 0.97217107

00:08:34.585 --> 00:08:35.785 but there but there is

NOTE Confidence: 0.97217107

00:08:35.785 --> 00:08:37.245 something clinically actionable.

NOTE Confidence: 0.96416086

00:08:37.625 --> 00:08:38.665 And and if I can,

NOTE Confidence: 0.96416086

00:08:38.665 --> 00:08:40.105 you know, I I welcome

NOTE Confidence: 0.96416086

00:08:40.105 --> 00:08:41.545 your your comments on on

NOTE Confidence: 0.96416086

00:08:41.545 --> 00:08:42.345 whether or not I I

NOTE Confidence: 0.96416086

00:08:42.345 --> 00:08:43.889 prove that point. But in

NOTE Confidence: 0.96416086

00:08:43.889 --> 00:08:45.170 giving this talk, I I

NOTE Confidence: 0.96416086

00:08:45.170 --> 00:08:46.209 I tried to think what

NOTE Confidence: 0.96416086

00:08:46.209 --> 00:08:47.250 can I really tell you

NOTE Confidence: 0.96416086

00:08:47.250 --> 00:08:48.529 about genetics that you haven't

NOTE Confidence: 0.96416086

00:08:48.529 --> 00:08:50.769 already heard? Right? This Yale

NOTE Confidence: 0.96416086

00:08:50.769 --> 00:08:51.970 here with Rick Lifton is

NOTE Confidence: 0.96416086

00:08:51.970 --> 00:08:53.089 sort of the birthplace of

NOTE Confidence: 0.96416086

00:08:53.089 --> 00:08:53.910 both Mendelian

NOTE Confidence: 0.95614755

00:08:54.449 --> 00:08:56.129 and common varying genetics. And

NOTE Confidence: 0.95614755

00:08:56.129 --> 00:08:58.045 probably for, you know the

NOTE Confidence: 0.95614755

00:08:58.045 --> 00:08:59.565 last twenty five years you've

NOTE Confidence: 0.95614755

00:08:59.565 --> 00:09:00.925 heard about the promise of

NOTE Confidence: 0.95614755

00:09:00.925 --> 00:09:02.445 human genetics to change how

NOTE Confidence: 0.95614755

00:09:02.445 --> 00:09:04.445 we treat patients right. From

NOTE Confidence: 0.95614755

00:09:04.445 --> 00:09:05.485 you know just from Rick

NOTE Confidence: 0.95614755

00:09:05.485 --> 00:09:06.865 Lifton's career itself

NOTE Confidence: 0.9342477

00:09:07.645 --> 00:09:09.005 you know a solid ten

NOTE Confidence: 0.9342477

00:09:09.005 --> 00:09:11.105 years twenty years of discovery

NOTE Confidence: 0.9342477

00:09:11.165 --> 00:09:13.245 in the the Mendelian drivers

NOTE Confidence: 0.9342477

00:09:13.245 --> 00:09:14.120 of hypertension,

NOTE Confidence: 0.98442286

00:09:14.660 --> 00:09:16.200 and then in the GWAS

NOTE Confidence: 0.9410842

00:09:16.820 --> 00:09:17.880 studies for hypertension,

NOTE Confidence: 0.98955464

00:09:18.340 --> 00:09:19.540 and then he even did

NOTE Confidence: 0.98955464

00:09:19.540 --> 00:09:21.059 variant to function for one

NOTE Confidence: 0.98955464

00:09:21.059 --> 00:09:22.179 of the top loci for

NOTE Confidence: 0.98955464

00:09:22.179 --> 00:09:22.679 hypertension.

NOTE Confidence: 0.94656086

00:09:23.460 --> 00:09:25.220 And based on really his

NOTE Confidence: 0.94656086

00:09:25.220 --> 00:09:25.720 contributions

NOTE Confidence: 0.97989875

00:09:26.100 --> 00:09:27.455 to the field, you know,

NOTE Confidence: 0.97989875

00:09:27.455 --> 00:09:29.054 the the cover of of

NOTE Confidence: 0.97989875

00:09:29.054 --> 00:09:31.375 basically our famous journals always

NOTE Confidence: 0.97989875

00:09:31.375 --> 00:09:32.735 promise that, you know, the

NOTE Confidence: 0.97989875

00:09:32.735 --> 00:09:34.095 human genome and the genome

NOTE Confidence: 0.97989875

00:09:34.095 --> 00:09:36.015 revolution was coming, that we

NOTE Confidence: 0.97989875

00:09:36.015 --> 00:09:37.395 would be able to really

NOTE Confidence: 0.97989875

00:09:37.455 --> 00:09:38.975 deliver on the clinical impact

NOTE Confidence: 0.97989875

00:09:38.975 --> 00:09:39.870 of these findings.

NOTE Confidence: 0.9892053

00:09:40.270 --> 00:09:41.070 And here we are, you

NOTE Confidence: 0.9892053

00:09:41.070 --> 00:09:42.910 know, twenty five years after

NOTE Confidence: 0.9892053

00:09:42.910 --> 00:09:44.029 the sequencing of the human

NOTE Confidence: 0.9892053

00:09:44.029 --> 00:09:45.950 genome. And what what we

NOTE Confidence: 0.9892053

00:09:45.950 --> 00:09:47.390 promised was the genomic era

NOTE Confidence: 0.9892053

00:09:47.390 --> 00:09:48.429 of medicine was that we

NOTE Confidence: 0.9892053

00:09:48.429 --> 00:09:49.809 would have precision medicine

NOTE Confidence: 0.98911744

00:09:50.350 --> 00:09:52.110 from low cost genetic sequencing,

NOTE Confidence: 0.98911744

00:09:52.110 --> 00:09:53.730 and we'd have targeted therapies,

NOTE Confidence: 0.92608565

00:09:54.270 --> 00:09:55.845 early detection, and reclassification

NOTE Confidence: 0.99237674

00:09:56.245 --> 00:09:58.165 reclassification of diseases into genetic

NOTE Confidence: 0.99237674

00:09:58.165 --> 00:09:59.845 subtypes. Right? That was the

NOTE Confidence: 0.99237674

00:09:59.845 --> 00:10:01.204 promise we made when when

NOTE Confidence: 0.99237674

00:10:01.204 --> 00:10:02.504 the genome was sequenced.

NOTE Confidence: 0.9868525

00:10:03.365 --> 00:10:04.245 And I would say that,

NOTE Confidence: 0.9868525

00:10:04.245 --> 00:10:05.845 you know, as as my

NOTE Confidence: 0.9868525

00:10:05.845 --> 00:10:07.444 my friends, Tarek and Nihar,

NOTE Confidence: 0.9868525

00:10:07.444 --> 00:10:08.485 often tell me, maybe we

NOTE Confidence: 0.9868525

00:10:08.485 --> 00:10:10.030 haven't delivered on that promise

NOTE Confidence: 0.9868525

00:10:10.030 --> 00:10:11.350 as much as we we

NOTE Confidence: 0.9868525

00:10:11.350 --> 00:10:12.570 had hoped by now.

NOTE Confidence: 0.99315494

00:10:12.950 --> 00:10:15.290 There are certainly success stories

NOTE Confidence: 0.99315494

00:10:15.350 --> 00:10:16.870 in the application of genetics

NOTE Confidence: 0.99315494

00:10:16.870 --> 00:10:18.150 to clinical care, and I

NOTE Confidence: 0.99315494

00:10:18.150 --> 00:10:18.950 tried to put a few

NOTE Confidence: 0.99315494

00:10:18.950 --> 00:10:19.910 of them here. Right? And

NOTE Confidence: 0.99315494

00:10:19.910 --> 00:10:20.710 and a lot of these

NOTE Confidence: 0.99315494

00:10:20.710 --> 00:10:21.770 have Yale roots,

NOTE Confidence: 0.95547694

00:10:22.775 --> 00:10:24.855 particularly eGFR inhibitors for non

NOTE Confidence: 0.95547694

00:10:24.855 --> 00:10:26.635 small cell lung cancer. Right?

NOTE Confidence: 0.9560623

00:10:27.095 --> 00:10:28.375 You know, was a targeted

NOTE Confidence: 0.9560623

00:10:28.375 --> 00:10:30.075 therapy in the cancer realm.

NOTE Confidence: 0.9560623

00:10:30.135 --> 00:10:30.635 Pharmacogenomics

NOTE Confidence: 0.93070966

00:10:31.415 --> 00:10:33.175 for variants that affect warfarin

NOTE Confidence: 0.93070966

00:10:33.175 --> 00:10:33.675 metabolism.

NOTE Confidence: 0.96717834

00:10:34.215 --> 00:10:35.735 And then gene therapies. Right?

NOTE Confidence: 0.96717834

00:10:35.735 --> 00:10:37.970 Genetic correction for certain Mendelian

NOTE Confidence: 0.96717834

00:10:38.029 --> 00:10:38.529 diseases.

NOTE Confidence: 0.97456354

00:10:39.309 --> 00:10:40.350 But and, you know, this

NOTE Confidence: 0.97456354

00:10:40.350 --> 00:10:41.390 is this is from the

NOTE Confidence: 0.97456354

00:10:41.390 --> 00:10:42.370 popular press.

NOTE Confidence: 0.97576547

00:10:42.750 --> 00:10:44.510 The amount of genomic data

NOTE Confidence: 0.97576547

00:10:44.510 --> 00:10:46.670 is just increasing exponentially. This

NOTE Confidence: 0.97576547

00:10:46.670 --> 00:10:48.270 is just ancestry dot com

NOTE Confidence: 0.97576547

00:10:48.270 --> 00:10:49.425 and twenty three and me,

NOTE Confidence: 0.97576547

00:10:49.584 --> 00:10:50.625 and it went from, you

NOTE Confidence: 0.97576547

00:10:50.625 --> 00:10:51.985 know, maybe a million people

NOTE Confidence: 0.97576547

00:10:51.985 --> 00:10:53.125 in twenty thirteen

NOTE Confidence: 0.9486009

00:10:53.985 --> 00:10:55.505 to twenty five million people,

NOTE Confidence: 0.9486009

00:10:55.505 --> 00:10:56.865 like, twenty five x the

NOTE Confidence: 0.9486009

00:10:56.865 --> 00:10:58.245 number of genomic data.

NOTE Confidence: 0.9787084

00:10:58.945 --> 00:10:59.825 And so you would think

NOTE Confidence: 0.9787084

00:10:59.825 --> 00:11:00.945 that, you know, the data

NOTE Confidence: 0.9787084

00:11:00.945 --> 00:11:01.985 is there, so then the

NOTE Confidence: 0.9787084

00:11:01.985 --> 00:11:03.870 impact must be there. And

NOTE Confidence: 0.9787084

00:11:03.870 --> 00:11:04.990 I would say that I

NOTE Confidence: 0.9787084

00:11:04.990 --> 00:11:06.290 will admit that the revolution

NOTE Confidence: 0.9787084

00:11:06.429 --> 00:11:08.350 has been slow. For coronary

NOTE Confidence: 0.9787084

00:11:08.350 --> 00:11:08.850 disease,

NOTE Confidence: 0.9980032

00:11:09.550 --> 00:11:10.690 we've been successful

NOTE Confidence: 0.90245366

00:11:11.070 --> 00:11:13.230 at identifying data that we

NOTE Confidence: 0.90245366

00:11:13.230 --> 00:11:14.830 can analyze. Right? My mentor,

NOTE Confidence: 0.90245366

00:11:14.830 --> 00:11:15.570 say, Katharason,

NOTE Confidence: 0.96768475

00:11:16.029 --> 00:11:16.850 led genotyping

NOTE Confidence: 0.99481094

00:11:17.630 --> 00:11:19.144 and and applied it to

NOTE Confidence: 0.99481094

00:11:19.144 --> 00:11:20.584 genomic biobanks all over the

NOTE Confidence: 0.99481094

00:11:20.584 --> 00:11:22.824 world. Lipid lowering drugs have

NOTE Confidence: 0.99481094

00:11:22.824 --> 00:11:24.764 been supported by genetic data,

NOTE Confidence: 0.9961588

00:11:25.144 --> 00:11:26.985 but we don't use genetic

NOTE Confidence: 0.9961588

00:11:26.985 --> 00:11:28.425 risk scores to guide therapy.

NOTE Confidence: 0.9961588

00:11:28.425 --> 00:11:29.144 I think, you know, that's

NOTE Confidence: 0.9961588

00:11:29.144 --> 00:11:30.665 one of the major questions

NOTE Confidence: 0.9961588

00:11:30.665 --> 00:11:31.644 I've gotten today

NOTE Confidence: 0.9863209

00:11:31.950 --> 00:11:32.670 is that, you know, are

NOTE Confidence: 0.9863209

00:11:32.670 --> 00:11:33.710 you are you are you

NOTE Confidence: 0.9863209

00:11:33.710 --> 00:11:35.070 using genomic risk scores at

NOTE Confidence: 0.9863209

00:11:35.070 --> 00:11:35.950 all? Have they had any

NOTE Confidence: 0.9863209

00:11:35.950 --> 00:11:36.929 impact? And,

NOTE Confidence: 0.98384

00:11:38.590 --> 00:11:40.370 Eric Topol, right, made available

NOTE Confidence: 0.99057627

00:11:40.830 --> 00:11:41.570 this this,

NOTE Confidence: 0.9550057

00:11:42.670 --> 00:11:44.270 iPhone app, my gene rank,

NOTE Confidence: 0.9550057

00:11:44.270 --> 00:11:46.135 and this is my genomic

NOTE Confidence: 0.9550057

00:11:46.135 --> 00:11:47.495 risk score for coronary disease

NOTE Confidence: 0.9550057

00:11:47.495 --> 00:11:48.535 at the bottom right corner.

NOTE Confidence: 0.9550057

00:11:48.535 --> 00:11:49.655 So I'm in the ninety

NOTE Confidence: 0.9550057

00:11:49.655 --> 00:11:51.115 second point third percentile,

NOTE Confidence: 0.9731212

00:11:51.575 --> 00:11:52.695 which is humbling. Right? You

NOTE Confidence: 0.9731212

00:11:52.695 --> 00:11:53.335 know? So I'm I'm one

NOTE Confidence: 0.9731212

00:11:53.335 --> 00:11:54.135 of, you know, one of

NOTE Confidence: 0.9731212

00:11:54.135 --> 00:11:55.035 the, you know,

NOTE Confidence: 0.97346586

00:11:55.495 --> 00:11:57.255 highest genetic risk for coronary

NOTE Confidence: 0.97346586

00:11:57.255 --> 00:11:58.740 disease, And I don't do

NOTE Confidence: 0.97346586

00:11:58.740 --> 00:11:59.860 anything about that, and this

NOTE Confidence: 0.97346586

00:11:59.860 --> 00:12:01.160 is what I study every

NOTE Confidence: 0.97346586

00:12:01.220 --> 00:12:02.500 day. And so that's sort

NOTE Confidence: 0.97346586

00:12:02.500 --> 00:12:03.780 of the challenge that I

NOTE Confidence: 0.97346586

00:12:03.780 --> 00:12:04.980 I was excited to tackle

NOTE Confidence: 0.97346586

00:12:04.980 --> 00:12:06.020 when I started my lab.

NOTE Confidence: 0.97346586

00:12:06.020 --> 00:12:07.300 And certainly, you know, this

NOTE Confidence: 0.97346586

00:12:07.300 --> 00:12:09.620 slide is is certainly relevant

NOTE Confidence: 0.97346586

00:12:09.620 --> 00:12:11.059 is, you know, despite years

NOTE Confidence: 0.97346586

00:12:11.059 --> 00:12:12.740 of progress in coronary disease

NOTE Confidence: 0.97346586

00:12:12.740 --> 00:12:13.635 and heart failure,

NOTE Confidence: 0.94611704

00:12:14.115 --> 00:12:15.475 the last ten years have

NOTE Confidence: 0.94611704

00:12:15.475 --> 00:12:17.815 seen these curves reverse direction.

NOTE Confidence: 0.94611704

00:12:17.875 --> 00:12:20.295 So coronary artery disease increasing

NOTE Confidence: 0.94611704

00:12:20.355 --> 00:12:20.855 prevalence

NOTE Confidence: 0.96748734

00:12:21.155 --> 00:12:22.275 in just the last five

NOTE Confidence: 0.96748734

00:12:22.275 --> 00:12:24.115 years and heart failure certainly

NOTE Confidence: 0.96748734

00:12:24.115 --> 00:12:25.635 over the last fifteen years

NOTE Confidence: 0.96748734

00:12:25.635 --> 00:12:26.615 increasing prevalence.

NOTE Confidence: 0.9991945

00:12:27.395 --> 00:12:28.900 So the outline for what

NOTE Confidence: 0.9991945

00:12:28.900 --> 00:12:30.580 I wanna present today is

NOTE Confidence: 0.9991945

00:12:30.580 --> 00:12:32.179 really three stories that come

NOTE Confidence: 0.9991945

00:12:32.179 --> 00:12:33.400 from the work we're doing.

NOTE Confidence: 0.9892593

00:12:33.780 --> 00:12:34.900 The first is I wanna

NOTE Confidence: 0.9892593

00:12:34.900 --> 00:12:36.740 review the promise and perils

NOTE Confidence: 0.9892593

00:12:36.740 --> 00:12:38.280 of these genetic risk scores.

NOTE Confidence: 0.9892593

00:12:38.340 --> 00:12:39.540 They've been around for about

NOTE Confidence: 0.9892593

00:12:39.540 --> 00:12:41.059 ten years. You'll you'll read

NOTE Confidence: 0.9892593

00:12:41.059 --> 00:12:43.184 on Twitter or x that,

NOTE Confidence: 0.9892593

00:12:43.505 --> 00:12:44.785 people are now making these

NOTE Confidence: 0.9892593

00:12:44.785 --> 00:12:46.545 clinically available, and I'm certain

NOTE Confidence: 0.9892593

00:12:46.545 --> 00:12:47.425 Yale will be one of

NOTE Confidence: 0.9892593

00:12:47.425 --> 00:12:48.705 the places that's the first

NOTE Confidence: 0.9892593

00:12:48.705 --> 00:12:49.925 to adopt these things,

NOTE Confidence: 0.9781753

00:12:50.385 --> 00:12:51.505 but there are pros and

NOTE Confidence: 0.9781753

00:12:51.505 --> 00:12:53.184 cons. The second is that

NOTE Confidence: 0.9781753

00:12:53.184 --> 00:12:54.145 my lab as a basic

NOTE Confidence: 0.9781753

00:12:54.145 --> 00:12:55.105 science lab is trying to

NOTE Confidence: 0.9781753

00:12:55.105 --> 00:12:56.900 provide a mechanistic approach to

NOTE Confidence: 0.9781753

00:12:56.900 --> 00:12:58.360 these polygenic risk scores.

NOTE Confidence: 0.9994977

00:12:58.740 --> 00:13:00.500 I firmly believe that the

NOTE Confidence: 0.9994977

00:13:00.500 --> 00:13:02.279 future of genetic risk prediction

NOTE Confidence: 0.9752542

00:13:02.660 --> 00:13:04.020 is at the intersection of

NOTE Confidence: 0.9752542

00:13:04.020 --> 00:13:05.160 genetics and function.

NOTE Confidence: 0.9423392

00:13:05.860 --> 00:13:06.839 And then finally,

NOTE Confidence: 0.9906865

00:13:07.300 --> 00:13:08.339 my focus has been on

NOTE Confidence: 0.9906865

00:13:08.339 --> 00:13:10.120 one cell type that's endothelial

NOTE Confidence: 0.9906865

00:13:10.179 --> 00:13:11.434 cells, and I'll I'll show

NOTE Confidence: 0.9906865

00:13:11.434 --> 00:13:12.395 some of the data that

NOTE Confidence: 0.9906865

00:13:12.395 --> 00:13:13.215 supports that.

NOTE Confidence: 0.98123026

00:13:13.595 --> 00:13:14.795 So first, the promise and

NOTE Confidence: 0.98123026

00:13:14.795 --> 00:13:16.495 perils of genomic risk scores.

NOTE Confidence: 0.9711765

00:13:17.355 --> 00:13:19.115 So I focused on coronary

NOTE Confidence: 0.9711765

00:13:19.115 --> 00:13:20.475 artery disease, but genomic risk

NOTE Confidence: 0.9711765

00:13:20.475 --> 00:13:22.175 scores have developed for AFib,

NOTE Confidence: 0.9711765

00:13:22.235 --> 00:13:23.675 for breast cancer, for all

NOTE Confidence: 0.9711765

00:13:23.675 --> 00:13:24.875 kinds of cancer, and other

NOTE Confidence: 0.9711765

00:13:24.875 --> 00:13:27.170 cardiovascular diseases as well. For

NOTE Confidence: 0.9711765

00:13:27.170 --> 00:13:29.410 coronary disease, right, we've got

NOTE Confidence: 0.9711765

00:13:29.410 --> 00:13:30.450 the kind of the most

NOTE Confidence: 0.9711765

00:13:30.450 --> 00:13:32.450 robust clinical data. The genomic

NOTE Confidence: 0.9711765

00:13:32.450 --> 00:13:33.570 data for coronary disease is

NOTE Confidence: 0.9711765

00:13:33.570 --> 00:13:35.750 the strongest because every biobank,

NOTE Confidence: 0.9711765

00:13:35.890 --> 00:13:36.850 the number one cause of

NOTE Confidence: 0.9711765

00:13:36.850 --> 00:13:38.150 death, the number one diagnosis

NOTE Confidence: 0.9711765

00:13:38.210 --> 00:13:38.870 is coronary

NOTE Confidence: 0.9898421

00:13:39.434 --> 00:13:40.395 disease. So at this point,

NOTE Confidence: 0.9898421

00:13:40.395 --> 00:13:41.515 we have over a million

NOTE Confidence: 0.9898421

00:13:41.515 --> 00:13:42.575 cases and controls.

NOTE Confidence: 0.99584717

00:13:43.035 --> 00:13:44.395 We are able to explain

NOTE Confidence: 0.99584717

00:13:44.395 --> 00:13:45.755 about fifty to sixty percent

NOTE Confidence: 0.99584717

00:13:45.755 --> 00:13:46.575 of the heritability,

NOTE Confidence: 0.930223

00:13:47.675 --> 00:13:49.135 through genetics, and

NOTE Confidence: 0.947982

00:13:49.675 --> 00:13:51.054 forty percent of that heritability

NOTE Confidence: 0.947982

00:13:51.195 --> 00:13:52.795 is captured by common variant

NOTE Confidence: 0.947982

00:13:52.795 --> 00:13:53.775 association studies.

NOTE Confidence: 0.9869807

00:13:54.490 --> 00:13:54.990 And,

NOTE Confidence: 0.96137553

00:13:55.450 --> 00:13:56.730 you know, the the common

NOTE Confidence: 0.96137553

00:13:56.730 --> 00:13:58.010 variant piece is what's sort

NOTE Confidence: 0.96137553

00:13:58.010 --> 00:13:59.050 of interesting. I'll get back

NOTE Confidence: 0.96137553

00:13:59.050 --> 00:14:00.030 to this later,

NOTE Confidence: 0.9987093

00:14:00.410 --> 00:14:00.910 but

NOTE Confidence: 0.9642987

00:14:01.370 --> 00:14:03.850 common variants often individually have

NOTE Confidence: 0.9642987

00:14:03.850 --> 00:14:04.990 small effect sizes,

NOTE Confidence: 0.97038203

00:14:05.370 --> 00:14:07.405 whereas rare variants, which were

NOTE Confidence: 0.97038203

00:14:07.405 --> 00:14:08.945 the focus of Rick Lifton's

NOTE Confidence: 0.97038203

00:14:09.165 --> 00:14:10.705 major impact in hypertension,

NOTE Confidence: 0.9769588

00:14:11.245 --> 00:14:12.684 have are are are obviously

NOTE Confidence: 0.9769588

00:14:12.684 --> 00:14:13.885 rare, but have a bigger

NOTE Confidence: 0.9769588

00:14:13.885 --> 00:14:16.045 effect size. But when you

NOTE Confidence: 0.9769588

00:14:16.045 --> 00:14:16.545 analyze

NOTE Confidence: 0.96095043

00:14:16.845 --> 00:14:18.205 millions of cases, you can

NOTE Confidence: 0.96095043

00:14:18.205 --> 00:14:19.585 find the power to identify

NOTE Confidence: 0.96095043

00:14:19.645 --> 00:14:21.485 these common variants. And so

NOTE Confidence: 0.96095043

00:14:21.485 --> 00:14:22.285 this is sort of a

NOTE Confidence: 0.96095043

00:14:22.285 --> 00:14:23.850 summary of the last fifteen

NOTE Confidence: 0.96095043

00:14:23.850 --> 00:14:25.210 years of GWAS studies for

NOTE Confidence: 0.96095043

00:14:25.210 --> 00:14:27.050 coronary disease. I joke that

NOTE Confidence: 0.96095043

00:14:27.050 --> 00:14:27.930 GWAS studies are sort of

NOTE Confidence: 0.96095043

00:14:27.930 --> 00:14:29.130 the gift that keeps on

NOTE Confidence: 0.96095043

00:14:29.130 --> 00:14:30.810 giving because we just add

NOTE Confidence: 0.96095043

00:14:30.810 --> 00:14:32.250 another cohort to the meta

NOTE Confidence: 0.96095043

00:14:32.250 --> 00:14:33.530 analysis and lo and behold,

NOTE Confidence: 0.96095043

00:14:33.530 --> 00:14:35.070 it's another high impact paper.

NOTE Confidence: 0.96095043

00:14:35.210 --> 00:14:36.570 But the very first GWAS

NOTE Confidence: 0.96095043

00:14:36.570 --> 00:14:37.770 study for coronary disease was

NOTE Confidence: 0.96095043

00:14:37.770 --> 00:14:39.285 conducted in Europe. Europe. Just

NOTE Confidence: 0.96095043

00:14:39.285 --> 00:14:41.045 three thousand cases, five thousand

NOTE Confidence: 0.96095043

00:14:41.045 --> 00:14:41.545 controls,

NOTE Confidence: 0.9524956

00:14:42.245 --> 00:14:43.925 and they identified three loci

NOTE Confidence: 0.9524956

00:14:43.925 --> 00:14:45.925 associated with coronary disease. Most

NOTE Confidence: 0.9524956

00:14:45.925 --> 00:14:47.605 recently in in Nature Genetics,

NOTE Confidence: 0.9524956

00:14:47.605 --> 00:14:49.285 we published the million heart

NOTE Confidence: 0.9524956

00:14:49.285 --> 00:14:51.045 study. Right? A million cases

NOTE Confidence: 0.9524956

00:14:51.045 --> 00:14:52.165 and controls. We're at two

NOTE Confidence: 0.9524956

00:14:52.165 --> 00:14:53.699 hundred and forty loci. And

NOTE Confidence: 0.9524956

00:14:53.699 --> 00:14:55.060 pretty soon, we're gonna publish

NOTE Confidence: 0.9524956

00:14:55.060 --> 00:14:56.420 a meta analysis with the

NOTE Confidence: 0.9524956

00:14:56.420 --> 00:14:58.180 million veterans program. We'll be

NOTE Confidence: 0.9524956

00:14:58.180 --> 00:14:59.699 at five hundred loci. Right?

NOTE Confidence: 0.9524956

00:14:59.699 --> 00:15:01.779 The there's diminishing returns on

NOTE Confidence: 0.9524956

00:15:01.779 --> 00:15:02.600 more genetic,

NOTE Confidence: 0.99705386

00:15:03.300 --> 00:15:04.360 analysis. Right?

NOTE Confidence: 0.9761548

00:15:05.454 --> 00:15:07.375 What was really exciting about

NOTE Confidence: 0.9761548

00:15:07.375 --> 00:15:08.815 the the GWAS that we

NOTE Confidence: 0.9761548

00:15:08.815 --> 00:15:09.695 did is that when you

NOTE Confidence: 0.9761548

00:15:09.695 --> 00:15:10.654 look at these two hundred

NOTE Confidence: 0.9761548

00:15:10.654 --> 00:15:11.795 and forty one loci,

NOTE Confidence: 0.97577035

00:15:12.415 --> 00:15:13.935 over eighty percent are not

NOTE Confidence: 0.97577035

00:15:13.935 --> 00:15:16.014 associated with LDL cholesterol. Right?

NOTE Confidence: 0.97577035

00:15:16.014 --> 00:15:17.615 So for coronary disease, really

NOTE Confidence: 0.97577035

00:15:17.615 --> 00:15:19.135 the only preventive therapy we

NOTE Confidence: 0.97577035

00:15:19.135 --> 00:15:20.755 have is lipid lowering therapy.

NOTE Confidence: 0.9842378

00:15:21.480 --> 00:15:23.080 But of the two hundred

NOTE Confidence: 0.9842378

00:15:23.080 --> 00:15:24.680 and forty one loci, only

NOTE Confidence: 0.9842378

00:15:24.680 --> 00:15:26.120 about twenty percent are associated

NOTE Confidence: 0.9842378

00:15:26.120 --> 00:15:28.220 with LDL cholesterol at all.

NOTE Confidence: 0.9842378

00:15:28.279 --> 00:15:30.040 Eighty percent are not at

NOTE Confidence: 0.9842378

00:15:30.040 --> 00:15:31.660 all associated with lipid cholesterol.

NOTE Confidence: 0.9598836

00:15:32.279 --> 00:15:33.399 And on the left, you

NOTE Confidence: 0.9598836

00:15:33.399 --> 00:15:34.920 see the the lipid related

NOTE Confidence: 0.9598836

00:15:34.920 --> 00:15:36.279 loci, and those are very

NOTE Confidence: 0.9598836

00:15:36.279 --> 00:15:38.394 hypothesis validating. Right? They're they're

NOTE Confidence: 0.9598836

00:15:38.394 --> 00:15:39.595 genes that we all recognize

NOTE Confidence: 0.9598836

00:15:39.595 --> 00:15:41.274 in the lipid metabolism pathway,

NOTE Confidence: 0.9598836

00:15:41.274 --> 00:15:43.195 LDL receptor, APO c three,

NOTE Confidence: 0.9598836

00:15:43.195 --> 00:15:45.695 PCSK nine, HMG choroid ductase.

NOTE Confidence: 0.9944246

00:15:46.154 --> 00:15:47.115 On the right is sort

NOTE Confidence: 0.9944246

00:15:47.115 --> 00:15:48.635 of alphabet soup. Right? These

NOTE Confidence: 0.9944246

00:15:48.635 --> 00:15:49.915 are all genes that we

NOTE Confidence: 0.9944246

00:15:49.915 --> 00:15:51.514 don't really link to coronary

NOTE Confidence: 0.9944246

00:15:51.514 --> 00:15:52.560 disease or treat.

NOTE Confidence: 0.9976553

00:15:53.040 --> 00:15:53.840 And and just to sort

NOTE Confidence: 0.9976553

00:15:53.840 --> 00:15:55.200 of drive home that point,

NOTE Confidence: 0.9976553

00:15:55.200 --> 00:15:57.120 the number of lipid therapies

NOTE Confidence: 0.9976553

00:15:57.120 --> 00:15:58.100 we have for prevention

NOTE Confidence: 0.9279427

00:15:58.480 --> 00:15:59.840 are statins, ezetimibe, p c

NOTE Confidence: 0.9279427

00:15:59.840 --> 00:16:01.040 s k nine inhibitors, and

NOTE Confidence: 0.9279427

00:16:01.040 --> 00:16:02.160 this is now an expanding

NOTE Confidence: 0.9279427

00:16:02.160 --> 00:16:02.660 list.

NOTE Confidence: 0.9782504

00:16:03.040 --> 00:16:04.800 But non lipid therapies is

NOTE Confidence: 0.9782504

00:16:04.800 --> 00:16:05.779 sort of a graveyard

NOTE Confidence: 0.9800847

00:16:06.160 --> 00:16:08.420 of unsuccessful trials and unsuccessful

NOTE Confidence: 0.904725

00:16:08.774 --> 00:16:09.274 therapies,

NOTE Confidence: 0.9790794

00:16:09.975 --> 00:16:11.254 each of which were very

NOTE Confidence: 0.9790794

00:16:11.254 --> 00:16:12.535 exciting at some point, but

NOTE Confidence: 0.9790794

00:16:12.535 --> 00:16:14.074 ultimately didn't amount to anything.

NOTE Confidence: 0.9743759

00:16:14.375 --> 00:16:15.975 So the motivation for, like,

NOTE Confidence: 0.9743759

00:16:15.975 --> 00:16:17.495 GWAS people like me was

NOTE Confidence: 0.9743759

00:16:17.495 --> 00:16:19.095 to to identify new drug

NOTE Confidence: 0.9743759

00:16:19.095 --> 00:16:21.514 targets. But that's been exceedingly

NOTE Confidence: 0.9796246

00:16:21.815 --> 00:16:23.254 slow as I'll I'll sort

NOTE Confidence: 0.9796246

00:16:23.254 --> 00:16:24.850 of get into, but we're

NOTE Confidence: 0.9796246

00:16:24.850 --> 00:16:26.470 very good at variant discovery,

NOTE Confidence: 0.9796246

00:16:26.610 --> 00:16:27.970 but function has only been

NOTE Confidence: 0.9796246

00:16:27.970 --> 00:16:29.330 identified for a handful of

NOTE Confidence: 0.9796246

00:16:29.330 --> 00:16:30.850 these variants. So a dozen

NOTE Confidence: 0.9796246

00:16:30.850 --> 00:16:31.730 of these two hundred and

NOTE Confidence: 0.9796246

00:16:31.730 --> 00:16:32.930 forty one are linked to

NOTE Confidence: 0.9796246

00:16:32.930 --> 00:16:34.530 any target gene or mechanism

NOTE Confidence: 0.9796246

00:16:34.530 --> 00:16:35.110 of action.

NOTE Confidence: 0.98347014

00:16:35.410 --> 00:16:36.370 And the reasons for that

NOTE Confidence: 0.98347014

00:16:36.370 --> 00:16:37.410 are that most of these

NOTE Confidence: 0.98347014

00:16:37.410 --> 00:16:39.250 variants are in noncoding DNA,

NOTE Confidence: 0.98347014

00:16:39.250 --> 00:16:40.185 so we don't know what

NOTE Confidence: 0.98347014

00:16:40.185 --> 00:16:41.385 gene they target or how

NOTE Confidence: 0.98347014

00:16:41.385 --> 00:16:42.585 they regulate it or in

NOTE Confidence: 0.98347014

00:16:42.585 --> 00:16:44.045 what cell type they're relevant.

NOTE Confidence: 0.98347014

00:16:44.345 --> 00:16:45.785 And that causal cell type

NOTE Confidence: 0.98347014

00:16:45.785 --> 00:16:47.225 for a complex disease is

NOTE Confidence: 0.98347014

00:16:47.225 --> 00:16:49.065 hard. Some diseases are driven

NOTE Confidence: 0.98347014

00:16:49.065 --> 00:16:50.105 by a single cell type,

NOTE Confidence: 0.98347014

00:16:50.105 --> 00:16:51.065 and the genetics is a

NOTE Confidence: 0.98347014

00:16:51.065 --> 00:16:51.965 little more straightforward.

NOTE Confidence: 0.96871775

00:16:52.580 --> 00:16:54.020 But for coronary disease, right,

NOTE Confidence: 0.96871775

00:16:54.020 --> 00:16:54.980 it could be any one

NOTE Confidence: 0.96871775

00:16:54.980 --> 00:16:55.940 of these cell types in

NOTE Confidence: 0.96871775

00:16:55.940 --> 00:16:57.860 the vascular wall, endothelial cells,

NOTE Confidence: 0.96871775

00:16:57.860 --> 00:16:59.480 vascular muscle cells, macrophages.

NOTE Confidence: 0.9875163

00:17:00.260 --> 00:17:02.180 And so, you know, when

NOTE Confidence: 0.9875163

00:17:02.180 --> 00:17:04.440 people take these individual variants

NOTE Confidence: 0.9875163

00:17:04.595 --> 00:17:06.435 from variant to function, it

NOTE Confidence: 0.9875163

00:17:06.435 --> 00:17:07.875 can be very powerful. And

NOTE Confidence: 0.9875163

00:17:07.875 --> 00:17:08.755 so here are some of

NOTE Confidence: 0.9875163

00:17:08.755 --> 00:17:10.375 my favorite examples, but,

NOTE Confidence: 0.9734452

00:17:10.994 --> 00:17:12.195 you know, the the most

NOTE Confidence: 0.9734452

00:17:12.195 --> 00:17:13.234 famous is b c l

NOTE Confidence: 0.9734452

00:17:13.234 --> 00:17:14.355 eleven a. So that was

NOTE Confidence: 0.9734452

00:17:14.355 --> 00:17:15.335 a single variant

NOTE Confidence: 0.9171109

00:17:15.635 --> 00:17:16.755 in the b c eleven

NOTE Confidence: 0.9171109

00:17:16.755 --> 00:17:17.155 a,

NOTE Confidence: 0.95120883

00:17:17.850 --> 00:17:19.130 gene in the promoter for

NOTE Confidence: 0.95120883

00:17:19.130 --> 00:17:20.570 that gene. That was associated

NOTE Confidence: 0.95120883

00:17:20.570 --> 00:17:21.950 with higher levels of hemoglobin

NOTE Confidence: 0.95120883

00:17:22.010 --> 00:17:23.450 f, and that is now

NOTE Confidence: 0.95120883

00:17:23.450 --> 00:17:24.109 a therapy

NOTE Confidence: 0.96855193

00:17:24.410 --> 00:17:26.010 that's being targeted for sickle

NOTE Confidence: 0.96855193

00:17:26.010 --> 00:17:27.530 cell disease. People have done

NOTE Confidence: 0.96855193

00:17:27.530 --> 00:17:28.250 this for all sort of

NOTE Confidence: 0.96855193

00:17:28.250 --> 00:17:29.550 colitis or obesity,

NOTE Confidence: 0.9947873

00:17:30.355 --> 00:17:31.634 but the power of these

NOTE Confidence: 0.9947873

00:17:31.634 --> 00:17:33.394 individual stories is now sort

NOTE Confidence: 0.9947873

00:17:33.394 --> 00:17:34.755 of they they take almost

NOTE Confidence: 0.9947873

00:17:34.755 --> 00:17:36.514 a decade to to to

NOTE Confidence: 0.9947873

00:17:36.514 --> 00:17:38.215 get through the experimental pipeline,

NOTE Confidence: 0.9947873

00:17:38.274 --> 00:17:39.315 and then they often don't

NOTE Confidence: 0.9947873

00:17:39.315 --> 00:17:40.375 go beyond that.

NOTE Confidence: 0.96122056

00:17:40.835 --> 00:17:42.274 So that's where polygenic risk

NOTE Confidence: 0.96122056

00:17:42.274 --> 00:17:43.740 scores come up is that

NOTE Confidence: 0.96122056

00:17:43.740 --> 00:17:45.420 instead of studying individual variants

NOTE Confidence: 0.96122056

00:17:45.420 --> 00:17:47.340 and their minuscule effects, why

NOTE Confidence: 0.96122056

00:17:47.340 --> 00:17:49.180 don't you just aggregate multiple

NOTE Confidence: 0.96122056

00:17:49.180 --> 00:17:50.700 risk variants and identify the

NOTE Confidence: 0.96122056

00:17:50.700 --> 00:17:52.540 highest risk parent patients for

NOTE Confidence: 0.96122056

00:17:52.540 --> 00:17:54.060 intervention? And that was always

NOTE Confidence: 0.96122056

00:17:54.060 --> 00:17:55.260 a hypothesis, but it was

NOTE Confidence: 0.96122056

00:17:55.260 --> 00:17:56.940 sort of underpowered until the

NOTE Confidence: 0.96122056

00:17:56.940 --> 00:17:58.545 GWAS data got big enough.

NOTE Confidence: 0.96122056

00:17:58.705 --> 00:17:59.505 And so this was from

NOTE Confidence: 0.96122056

00:17:59.505 --> 00:18:00.465 my colleague when, you know,

NOTE Confidence: 0.96122056

00:18:00.465 --> 00:18:01.505 I was a postdoc, Amit

NOTE Confidence: 0.96122056

00:18:01.505 --> 00:18:02.545 Cara, who was in Sake's

NOTE Confidence: 0.96122056

00:18:02.545 --> 00:18:04.145 lab, published this, like, beautiful

NOTE Confidence: 0.96122056

00:18:04.145 --> 00:18:05.505 paper showing that, you know,

NOTE Confidence: 0.96122056

00:18:05.505 --> 00:18:06.465 at the ends of the

NOTE Confidence: 0.96122056

00:18:06.465 --> 00:18:07.984 spectrum, so the the people

NOTE Confidence: 0.96122056

00:18:07.984 --> 00:18:09.585 at the highest polygenic risk

NOTE Confidence: 0.96122056

00:18:09.585 --> 00:18:10.085 percentiles

NOTE Confidence: 0.9930053

00:18:10.545 --> 00:18:11.525 for heart disease,

NOTE Confidence: 0.97505593

00:18:12.030 --> 00:18:13.950 AFib, diabetes, breast cancer. In

NOTE Confidence: 0.97505593

00:18:13.950 --> 00:18:15.390 each case, the people at

NOTE Confidence: 0.97505593

00:18:15.390 --> 00:18:16.530 each end of the spectrum

NOTE Confidence: 0.97505593

00:18:16.590 --> 00:18:17.869 were showing the greatest risk.

NOTE Confidence: 0.97505593

00:18:17.869 --> 00:18:19.150 Right? You could aggregate these

NOTE Confidence: 0.97505593

00:18:19.150 --> 00:18:20.830 variants and find the people

NOTE Confidence: 0.97505593

00:18:20.830 --> 00:18:21.790 at greatest risk. And in

NOTE Confidence: 0.97505593

00:18:21.790 --> 00:18:23.390 fact, the people at the

NOTE Confidence: 0.97505593

00:18:23.390 --> 00:18:24.590 at the in the top

NOTE Confidence: 0.97505593

00:18:24.590 --> 00:18:25.410 five percent

NOTE Confidence: 0.97315794

00:18:25.785 --> 00:18:27.225 had equivalent risk to those

NOTE Confidence: 0.97315794

00:18:27.225 --> 00:18:28.905 people who had Mendelian mutations.

NOTE Confidence: 0.97315794

00:18:28.905 --> 00:18:31.005 So an LDL receptor familial

NOTE Confidence: 0.97315794

00:18:31.065 --> 00:18:31.565 hypercholesterolemia

NOTE Confidence: 0.9805174

00:18:32.585 --> 00:18:34.665 patient had the identical level

NOTE Confidence: 0.9805174

00:18:34.665 --> 00:18:35.705 of risk as someone who

NOTE Confidence: 0.9805174

00:18:35.705 --> 00:18:36.525 just inherited

NOTE Confidence: 0.960598

00:18:36.825 --> 00:18:38.505 three hundred small effect risk

NOTE Confidence: 0.960598

00:18:38.505 --> 00:18:40.605 variants in LDL receptor pathways.

NOTE Confidence: 0.99829453

00:18:41.250 --> 00:18:41.910 More recently,

NOTE Confidence: 0.98693156

00:18:42.770 --> 00:18:44.210 they have improved this and

NOTE Confidence: 0.98693156

00:18:44.210 --> 00:18:45.570 show that there's even greater

NOTE Confidence: 0.98693156

00:18:45.570 --> 00:18:47.830 predictive capacity with these even

NOTE Confidence: 0.98693156

00:18:47.890 --> 00:18:49.670 improved polygenic risk scores.

NOTE Confidence: 0.999342

00:18:50.050 --> 00:18:50.550 But

NOTE Confidence: 0.9922451

00:18:51.090 --> 00:18:51.970 at this point, you know,

NOTE Confidence: 0.9922451

00:18:51.970 --> 00:18:53.170 now five years after that

NOTE Confidence: 0.9922451

00:18:53.170 --> 00:18:55.090 paper, we we have this

NOTE Confidence: 0.9922451

00:18:55.090 --> 00:18:57.575 promise for polygenic risk scores

NOTE Confidence: 0.9922451

00:18:57.635 --> 00:18:58.455 that they could

NOTE Confidence: 0.8807637

00:18:59.155 --> 00:19:01.015 provide early detection of risk.

NOTE Confidence: 0.955953

00:19:01.395 --> 00:19:03.075 They could inform treatment decision

NOTE Confidence: 0.955953

00:19:03.075 --> 00:19:04.675 making, and they maybe could

NOTE Confidence: 0.955953

00:19:04.675 --> 00:19:06.135 be relevant in drug development,

NOTE Confidence: 0.955953

00:19:06.195 --> 00:19:07.475 right, for clinical trials. You

NOTE Confidence: 0.955953

00:19:07.475 --> 00:19:08.915 could enrich patients using these

NOTE Confidence: 0.955953

00:19:08.915 --> 00:19:09.415 scores.

NOTE Confidence: 0.9616442

00:19:10.109 --> 00:19:11.470 But the perils are well

NOTE Confidence: 0.9616442

00:19:11.470 --> 00:19:13.070 described too that there's limited

NOTE Confidence: 0.9616442

00:19:13.070 --> 00:19:14.130 predictive power.

NOTE Confidence: 0.98349667

00:19:14.670 --> 00:19:16.990 There's sometimes no benefit beyond

NOTE Confidence: 0.98349667

00:19:16.990 --> 00:19:17.490 nontraditional

NOTE Confidence: 0.99420285

00:19:17.790 --> 00:19:19.570 risk factors. Right? The additive

NOTE Confidence: 0.99420285

00:19:19.710 --> 00:19:21.390 power of these beyond just

NOTE Confidence: 0.99420285

00:19:21.390 --> 00:19:22.369 using age,

NOTE Confidence: 0.99882424

00:19:22.670 --> 00:19:23.170 race,

NOTE Confidence: 0.9645224

00:19:24.095 --> 00:19:25.375 sex, and, you know, with,

NOTE Confidence: 0.9645224

00:19:25.695 --> 00:19:27.535 hypertension and cholesterol numbers. Right?

NOTE Confidence: 0.9645224

00:19:27.535 --> 00:19:29.234 Just the Framingham risk score

NOTE Confidence: 0.92174035

00:19:29.775 --> 00:19:31.695 plus genetics. There's a minimal

NOTE Confidence: 0.92174035

00:19:31.695 --> 00:19:33.234 additive predictive value,

NOTE Confidence: 0.9994129

00:19:33.775 --> 00:19:35.795 and treatment interactions are unproven.

NOTE Confidence: 0.9970052

00:19:36.480 --> 00:19:37.220 And so,

NOTE Confidence: 0.985816

00:19:37.680 --> 00:19:38.960 one of my mentors, Tommy

NOTE Confidence: 0.985816

00:19:38.960 --> 00:19:40.740 Wang, right, published this editorial

NOTE Confidence: 0.985816

00:19:40.800 --> 00:19:41.619 where he basically

NOTE Confidence: 0.9685199

00:19:41.920 --> 00:19:43.760 just took polygenic risk scores

NOTE Confidence: 0.9685199

00:19:43.760 --> 00:19:44.960 to task. He said genetic

NOTE Confidence: 0.9685199

00:19:44.960 --> 00:19:46.080 risk scores for cancer are

NOTE Confidence: 0.9685199

00:19:46.080 --> 00:19:46.580 unique

NOTE Confidence: 0.9749448

00:19:46.880 --> 00:19:47.859 since they identify

NOTE Confidence: 0.97316235

00:19:48.285 --> 00:19:50.205 specific mechanisms of disease. Right?

NOTE Confidence: 0.97316235

00:19:50.205 --> 00:19:52.045 Whereas for CAD, it's just

NOTE Confidence: 0.97316235

00:19:52.045 --> 00:19:53.405 a different set point for

NOTE Confidence: 0.97316235

00:19:53.405 --> 00:19:54.925 the current therapies. Right? You

NOTE Confidence: 0.97316235

00:19:54.925 --> 00:19:56.285 just are just treating people

NOTE Confidence: 0.97316235

00:19:56.285 --> 00:19:57.484 at different levels of the

NOTE Confidence: 0.97316235

00:19:57.484 --> 00:19:58.525 same therapy. I thought that

NOTE Confidence: 0.97316235

00:19:58.525 --> 00:19:59.725 was a a a pretty

NOTE Confidence: 0.97316235

00:19:59.725 --> 00:20:01.484 biting indictment of polygenic risk

NOTE Confidence: 0.97316235

00:20:01.484 --> 00:20:01.984 scores.

NOTE Confidence: 0.9824919

00:20:02.340 --> 00:20:03.299 And and, you know, and

NOTE Confidence: 0.9824919

00:20:03.299 --> 00:20:04.820 I'm excited about them. But

NOTE Confidence: 0.9824919

00:20:04.820 --> 00:20:05.940 his point was that for

NOTE Confidence: 0.9824919

00:20:05.940 --> 00:20:07.059 cancer, right, if you find

NOTE Confidence: 0.9824919

00:20:07.059 --> 00:20:07.799 a pathway,

NOTE Confidence: 0.989586

00:20:08.179 --> 00:20:09.400 like a, you know, BRCA

NOTE Confidence: 0.989586

00:20:09.619 --> 00:20:11.460 one pathway, then you would

NOTE Confidence: 0.989586

00:20:11.460 --> 00:20:13.640 target therapies that are specific

NOTE Confidence: 0.989586

00:20:13.700 --> 00:20:14.600 to that pathway.

NOTE Confidence: 0.97737706

00:20:15.059 --> 00:20:16.755 But for coronary disease, we

NOTE Confidence: 0.97737706

00:20:16.755 --> 00:20:18.115 haven't used these scores to

NOTE Confidence: 0.97737706

00:20:18.115 --> 00:20:20.435 identify biologically relevant pathways. And

NOTE Confidence: 0.97737706

00:20:20.435 --> 00:20:21.715 so I just repeat this

NOTE Confidence: 0.97737706

00:20:21.715 --> 00:20:23.875 slide. I'm super motivated to

NOTE Confidence: 0.97737706

00:20:23.875 --> 00:20:25.234 find the pathways that are

NOTE Confidence: 0.97737706

00:20:25.234 --> 00:20:26.994 relevant to someone who has

NOTE Confidence: 0.97737706

00:20:26.994 --> 00:20:28.835 a high polygenic risk. So

NOTE Confidence: 0.97737706

00:20:28.835 --> 00:20:29.635 I sort of took this

NOTE Confidence: 0.97737706

00:20:29.635 --> 00:20:30.915 as a challenge for my

NOTE Confidence: 0.97737706

00:20:30.915 --> 00:20:33.080 lab. Is that can we

NOTE Confidence: 0.97737706

00:20:33.080 --> 00:20:34.380 provide a better pathologic

NOTE Confidence: 0.8003541

00:20:34.680 --> 00:20:36.300 understanding of CAD risk variants

NOTE Confidence: 0.9868428

00:20:36.920 --> 00:20:38.760 to improve genetic risk prediction

NOTE Confidence: 0.9868428

00:20:38.760 --> 00:20:40.520 and then guide targeted therapies

NOTE Confidence: 0.9868428

00:20:40.520 --> 00:20:41.320 one day? That's, like, the

NOTE Confidence: 0.9868428

00:20:41.320 --> 00:20:42.600 ultimate goal of all this

NOTE Confidence: 0.9868428

00:20:42.600 --> 00:20:43.100 work.

NOTE Confidence: 0.97624105

00:20:43.654 --> 00:20:45.174 And so I I sort

NOTE Confidence: 0.97624105

00:20:45.174 --> 00:20:46.135 of come to my second

NOTE Confidence: 0.97624105

00:20:46.135 --> 00:20:47.335 approach is is how do

NOTE Confidence: 0.97624105

00:20:47.335 --> 00:20:48.554 we do this? And so

NOTE Confidence: 0.97624105

00:20:48.615 --> 00:20:49.654 I'd say that one of

NOTE Confidence: 0.97624105

00:20:49.654 --> 00:20:51.335 the more exciting things about

NOTE Confidence: 0.97624105

00:20:51.335 --> 00:20:52.455 genetics in the last ten

NOTE Confidence: 0.97624105

00:20:52.455 --> 00:20:53.494 years, and and I I

NOTE Confidence: 0.97624105

00:20:53.575 --> 00:20:54.534 I'm I'm sort of on

NOTE Confidence: 0.97624105

00:20:54.534 --> 00:20:55.815 my soapbox about this with

NOTE Confidence: 0.97624105

00:20:55.815 --> 00:20:57.540 every meeting I've I've had

NOTE Confidence: 0.97624105

00:20:57.840 --> 00:20:59.700 is that now functional genomics

NOTE Confidence: 0.99299467

00:21:00.080 --> 00:21:01.540 is can be highly systematized.

NOTE Confidence: 0.9893255

00:21:02.240 --> 00:21:04.500 So GWAS was a powerful

NOTE Confidence: 0.9893255

00:21:04.560 --> 00:21:07.140 technology because sequencing got cheap,

NOTE Confidence: 0.9893255

00:21:07.359 --> 00:21:08.400 and you could go to

NOTE Confidence: 0.9893255

00:21:08.400 --> 00:21:09.680 every biobank in the world

NOTE Confidence: 0.9893255

00:21:09.680 --> 00:21:11.600 and genotype everyone for twenty

NOTE Confidence: 0.9893255

00:21:11.600 --> 00:21:12.580 dollars a sample.

NOTE Confidence: 0.9936663

00:21:13.174 --> 00:21:14.535 But you couldn't study the

NOTE Confidence: 0.9936663

00:21:14.535 --> 00:21:16.375 biologic effect of thousands of

NOTE Confidence: 0.9936663

00:21:16.375 --> 00:21:17.835 variants at that price.

NOTE Confidence: 0.9941394

00:21:18.215 --> 00:21:20.155 But with pooled CRISPR technology

NOTE Confidence: 0.9941394

00:21:20.455 --> 00:21:21.994 and single cell RNA sequencing,

NOTE Confidence: 0.95365906

00:21:22.695 --> 00:21:24.135 you can basically do GWAS

NOTE Confidence: 0.95365906

00:21:24.135 --> 00:21:25.415 in a dish. You can

NOTE Confidence: 0.95365906

00:21:25.415 --> 00:21:27.174 study the effect of millions

NOTE Confidence: 0.95365906

00:21:27.174 --> 00:21:27.835 of variants

NOTE Confidence: 0.890367

00:21:28.440 --> 00:21:30.279 individually in individual cells. And

NOTE Confidence: 0.890367

00:21:30.279 --> 00:21:31.559 so that technology is called

NOTE Confidence: 0.890367

00:21:31.559 --> 00:21:32.919 PerturbSeq. It was developed in

NOTE Confidence: 0.890367

00:21:32.919 --> 00:21:34.460 a Viva Gev's lab in

NOTE Confidence: 0.890367

00:21:34.519 --> 00:21:35.340 twenty sixteen.

NOTE Confidence: 0.9585883

00:21:36.039 --> 00:21:37.880 And I sometimes joke that

NOTE Confidence: 0.9585883

00:21:37.880 --> 00:21:39.080 at the Broad Institute where

NOTE Confidence: 0.9585883

00:21:39.080 --> 00:21:40.279 this was developed, there were

NOTE Confidence: 0.9585883

00:21:40.279 --> 00:21:41.799 two kinda hot technologies at

NOTE Confidence: 0.9585883

00:21:41.799 --> 00:21:42.835 the time. There was CRISPR

NOTE Confidence: 0.9585883

00:21:42.835 --> 00:21:43.875 editing and there were single

NOTE Confidence: 0.9585883

00:21:43.875 --> 00:21:44.935 cell RNA sequencing.

NOTE Confidence: 0.9637597

00:21:45.235 --> 00:21:46.195 So why not just combine

NOTE Confidence: 0.9637597

00:21:46.195 --> 00:21:47.235 them? Right? Just do them

NOTE Confidence: 0.9637597

00:21:47.235 --> 00:21:48.115 together. And that's sort of

NOTE Confidence: 0.9637597

00:21:48.115 --> 00:21:49.395 what this is, is you

NOTE Confidence: 0.9637597

00:21:49.395 --> 00:21:50.435 take a pool of cells,

NOTE Confidence: 0.9637597

00:21:50.435 --> 00:21:51.575 a million cells.

NOTE Confidence: 0.9495796

00:21:52.115 --> 00:21:53.155 You target them with a

NOTE Confidence: 0.9495796

00:21:53.155 --> 00:21:55.555 lentiviral libraries that introduces different

NOTE Confidence: 0.9495796

00:21:55.555 --> 00:21:57.179 CRISPR guide RNAs. Then you

NOTE Confidence: 0.9495796

00:21:57.179 --> 00:21:58.940 do single cell RNA sequencing

NOTE Confidence: 0.9495796

00:21:58.940 --> 00:21:59.899 of all that pool of

NOTE Confidence: 0.9495796

00:21:59.899 --> 00:22:00.399 cells.

NOTE Confidence: 0.9798821

00:22:00.779 --> 00:22:02.220 And in that sequencing, you

NOTE Confidence: 0.9798821

00:22:02.220 --> 00:22:04.059 not only find which CRISPR

NOTE Confidence: 0.9798821

00:22:04.059 --> 00:22:05.179 got into which cells, you're

NOTE Confidence: 0.9798821

00:22:05.179 --> 00:22:06.700 finding out which gene is

NOTE Confidence: 0.9798821

00:22:06.700 --> 00:22:08.220 knocked out, but you're finding

NOTE Confidence: 0.9798821

00:22:08.220 --> 00:22:09.899 the transcriptional effect of that

NOTE Confidence: 0.9798821

00:22:09.899 --> 00:22:12.005 knockdown. Right? And so people

NOTE Confidence: 0.9798821

00:22:12.005 --> 00:22:13.284 have been doing these pooled

NOTE Confidence: 0.9798821

00:22:13.284 --> 00:22:15.205 CRISPR screens for years for

NOTE Confidence: 0.9798821

00:22:15.205 --> 00:22:16.804 cancer therapy. They basically knock

NOTE Confidence: 0.9798821

00:22:16.804 --> 00:22:17.684 down every gene in the

NOTE Confidence: 0.9798821

00:22:17.684 --> 00:22:18.645 genome and then just see

NOTE Confidence: 0.9798821

00:22:18.645 --> 00:22:19.625 which cells grow.

NOTE Confidence: 0.9854084

00:22:20.325 --> 00:22:21.605 You know, they evade the

NOTE Confidence: 0.9854084

00:22:21.605 --> 00:22:22.965 the the therapy. So the

NOTE Confidence: 0.9854084

00:22:22.965 --> 00:22:24.164 first CRISPR screen was done

NOTE Confidence: 0.9854084

00:22:24.164 --> 00:22:24.904 for vemurafenib,

NOTE Confidence: 0.9930627

00:22:25.619 --> 00:22:27.240 which is a melanoma therapy.

NOTE Confidence: 0.9930627

00:22:27.380 --> 00:22:28.660 And so patients who get

NOTE Confidence: 0.9930627

00:22:28.660 --> 00:22:30.100 vemurafenib, there's a high level

NOTE Confidence: 0.9930627

00:22:30.100 --> 00:22:31.480 of resistance to vemurafenib.

NOTE Confidence: 0.99264944

00:22:32.260 --> 00:22:32.660 And,

NOTE Confidence: 0.97428095

00:22:33.140 --> 00:22:34.260 they did the first CRISPR

NOTE Confidence: 0.97428095

00:22:34.260 --> 00:22:36.020 screen to see which genes

NOTE Confidence: 0.97428095

00:22:36.020 --> 00:22:37.555 are mediating that resistance. So

NOTE Confidence: 0.97428095

00:22:37.555 --> 00:22:39.255 the cells that survive emirafenib

NOTE Confidence: 0.95695686

00:22:39.715 --> 00:22:41.095 are are mediating resistance.

NOTE Confidence: 0.97167903

00:22:41.475 --> 00:22:42.994 For coronary disease, we don't

NOTE Confidence: 0.97167903

00:22:42.994 --> 00:22:44.275 have a phenotype like that.

NOTE Confidence: 0.97167903

00:22:44.275 --> 00:22:45.555 Right? Like, for cancer, it's

NOTE Confidence: 0.97167903

00:22:45.555 --> 00:22:47.475 obviously which cells grow. For

NOTE Confidence: 0.97167903

00:22:47.475 --> 00:22:48.675 coronary disease, if we had

NOTE Confidence: 0.97167903

00:22:48.675 --> 00:22:49.410 to just prioritize,

NOTE Confidence: 0.8542681

00:22:54.690 --> 00:22:55.970 lamp post with this current

NOTE Confidence: 0.8542681

00:22:55.970 --> 00:22:57.410 screens we do. But with

NOTE Confidence: 0.8542681

00:22:57.410 --> 00:22:57.910 PerturbSeq,

NOTE Confidence: 0.97006226

00:22:58.290 --> 00:23:00.050 we're unbiased. We're just looking

NOTE Confidence: 0.97006226

00:23:00.050 --> 00:23:01.570 at the effects in in

NOTE Confidence: 0.97006226

00:23:01.570 --> 00:23:02.070 transcriptional

NOTE Confidence: 0.9859384

00:23:02.450 --> 00:23:03.990 space. And so,

NOTE Confidence: 0.9696039

00:23:04.304 --> 00:23:05.585 the Ragev Lab had applied

NOTE Confidence: 0.9696039

00:23:05.585 --> 00:23:07.424 this technology to fifty, sixty,

NOTE Confidence: 0.9696039

00:23:07.424 --> 00:23:08.965 seventy genes at a time,

NOTE Confidence: 0.9696039

00:23:09.184 --> 00:23:10.465 but we had thought, why

NOTE Confidence: 0.9696039

00:23:10.465 --> 00:23:11.424 don't we just do this

NOTE Confidence: 0.9696039

00:23:11.424 --> 00:23:12.644 for all the genes

NOTE Confidence: 0.9054334

00:23:12.945 --> 00:23:13.904 that are close to all

NOTE Confidence: 0.9054334

00:23:13.904 --> 00:23:15.585 the coronary artery disease GWAS

NOTE Confidence: 0.9054334

00:23:15.585 --> 00:23:16.085 loci?

NOTE Confidence: 0.98091483

00:23:16.669 --> 00:23:17.630 So when I started my

NOTE Confidence: 0.98091483

00:23:17.630 --> 00:23:18.909 lab, the first thing I

NOTE Confidence: 0.98091483

00:23:18.909 --> 00:23:20.210 did was made a library

NOTE Confidence: 0.98091483

00:23:20.270 --> 00:23:21.150 of all the genes that

NOTE Confidence: 0.98091483

00:23:21.150 --> 00:23:22.510 we wanted to study, the

NOTE Confidence: 0.98091483

00:23:22.510 --> 00:23:23.630 the two thousand genes we

NOTE Confidence: 0.98091483

00:23:23.630 --> 00:23:25.150 wanted to knock down. And

NOTE Confidence: 0.98091483

00:23:25.150 --> 00:23:26.750 so we built this library

NOTE Confidence: 0.98091483

00:23:26.750 --> 00:23:27.869 kind of by hand, and

NOTE Confidence: 0.98091483

00:23:27.869 --> 00:23:29.150 we took all genes within

NOTE Confidence: 0.98091483

00:23:29.150 --> 00:23:30.990 a megabase of every coronary

NOTE Confidence: 0.98091483

00:23:30.990 --> 00:23:32.884 artery disease GWAS locus, and

NOTE Confidence: 0.98091483

00:23:32.884 --> 00:23:34.085 that ended up being three

NOTE Confidence: 0.98091483

00:23:34.164 --> 00:23:35.845 thirteen hundred genes. Then we

NOTE Confidence: 0.98091483

00:23:35.845 --> 00:23:37.044 tried to include genes that

NOTE Confidence: 0.98091483

00:23:37.044 --> 00:23:38.804 were at other vascular relevant

NOTE Confidence: 0.98091483

00:23:38.804 --> 00:23:41.044 phenotypes, migraine headache, blood pressure

NOTE Confidence: 0.98091483

00:23:41.044 --> 00:23:42.965 control, blood clotting. That was

NOTE Confidence: 0.98091483

00:23:42.965 --> 00:23:44.264 another three hundred genes.

NOTE Confidence: 0.96393514

00:23:44.659 --> 00:23:45.940 Then we added four hundred

NOTE Confidence: 0.96393514

00:23:45.940 --> 00:23:47.460 genes and pathways we wanted

NOTE Confidence: 0.96393514

00:23:47.460 --> 00:23:47.960 overrepresented,

NOTE Confidence: 0.9873058

00:23:48.500 --> 00:23:50.019 like the VEGF pathway or

NOTE Confidence: 0.9873058

00:23:50.019 --> 00:23:51.779 the TGF beta pathway. Those

NOTE Confidence: 0.9873058

00:23:51.779 --> 00:23:52.419 turned out to be the

NOTE Confidence: 0.9873058

00:23:52.419 --> 00:23:54.260 wrong pathways to overrepresent, but,

NOTE Confidence: 0.9873058

00:23:54.260 --> 00:23:55.220 you know, so be it.

NOTE Confidence: 0.9873058

00:23:55.220 --> 00:23:55.940 And then we had three

NOTE Confidence: 0.9873058

00:23:55.940 --> 00:23:57.140 hundred negative control,

NOTE Confidence: 0.967212

00:23:57.539 --> 00:23:59.700 genes from inflammatory bowel disease

NOTE Confidence: 0.967212

00:23:59.700 --> 00:24:01.595 GWAS studies. A grand total

NOTE Confidence: 0.967212

00:24:01.595 --> 00:24:03.055 of twenty three hundred genes.

NOTE Confidence: 0.967212

00:24:03.195 --> 00:24:04.875 We had fifteen CRISPR guides

NOTE Confidence: 0.967212

00:24:04.875 --> 00:24:06.315 per gene, thirty seven thousand

NOTE Confidence: 0.967212

00:24:06.315 --> 00:24:07.515 six hundred and thirty seven

NOTE Confidence: 0.967212

00:24:07.515 --> 00:24:08.795 guides. So my first month

NOTE Confidence: 0.967212

00:24:08.795 --> 00:24:10.095 of being a PI,

NOTE Confidence: 0.94331133

00:24:10.875 --> 00:24:12.395 I and a technician hand

NOTE Confidence: 0.94331133

00:24:12.395 --> 00:24:13.755 cloned each of these guides

NOTE Confidence: 0.94331133

00:24:13.755 --> 00:24:15.570 into our lentiviral vector. Took

NOTE Confidence: 0.94331133

00:24:15.570 --> 00:24:16.369 us about a month of

NOTE Confidence: 0.94331133

00:24:16.369 --> 00:24:17.410 every day just like sort

NOTE Confidence: 0.94331133

00:24:17.410 --> 00:24:18.230 of, like,

NOTE Confidence: 0.9544608

00:24:18.929 --> 00:24:20.690 changing the bacterial media and

NOTE Confidence: 0.9544608

00:24:20.690 --> 00:24:21.830 things like that. But,

NOTE Confidence: 0.99299216

00:24:22.289 --> 00:24:23.090 we didn't know if this

NOTE Confidence: 0.99299216

00:24:23.090 --> 00:24:24.130 was gonna work. Right? We're

NOTE Confidence: 0.99299216

00:24:24.130 --> 00:24:26.070 gonna infect a million endothelial

NOTE Confidence: 0.99299216

00:24:26.210 --> 00:24:27.650 cells with thirty seven thousand

NOTE Confidence: 0.99299216

00:24:27.650 --> 00:24:28.770 guides and do single cell

NOTE Confidence: 0.99299216

00:24:28.770 --> 00:24:29.970 RNA sequencing on this big

NOTE Confidence: 0.99299216

00:24:29.970 --> 00:24:31.135 pool of cells, but it

NOTE Confidence: 0.99299216

00:24:31.135 --> 00:24:32.095 worked. Right? This is sort

NOTE Confidence: 0.99299216

00:24:32.095 --> 00:24:33.375 of a summary of the

NOTE Confidence: 0.99299216

00:24:33.375 --> 00:24:34.335 data we got. On the

NOTE Confidence: 0.99299216

00:24:34.335 --> 00:24:35.535 left, you see a cartoon

NOTE Confidence: 0.99299216

00:24:35.535 --> 00:24:36.335 of how we did the

NOTE Confidence: 0.99299216

00:24:36.335 --> 00:24:36.835 experiment.

NOTE Confidence: 0.9790813

00:24:37.135 --> 00:24:38.734 In the middle panel, each

NOTE Confidence: 0.9790813

00:24:38.734 --> 00:24:39.855 one of those dots on

NOTE Confidence: 0.9790813

00:24:39.855 --> 00:24:40.895 this UMAP plot is one

NOTE Confidence: 0.9790813

00:24:40.895 --> 00:24:41.775 of the cells that we

NOTE Confidence: 0.9790813

00:24:41.775 --> 00:24:43.375 perform single cell RNA sequencing

NOTE Confidence: 0.9790813

00:24:43.375 --> 00:24:44.350 on. And what you see

NOTE Confidence: 0.9790813

00:24:44.350 --> 00:24:45.390 is there's two hundred and

NOTE Confidence: 0.9790813

00:24:45.390 --> 00:24:46.909 fifteen thousand different dots, two

NOTE Confidence: 0.9790813

00:24:46.909 --> 00:24:48.369 hundred and fifteen thousand cells.

NOTE Confidence: 0.9873021

00:24:49.149 --> 00:24:50.350 Each one is targeted with

NOTE Confidence: 0.9873021

00:24:50.350 --> 00:24:51.390 a different guide RNA. We

NOTE Confidence: 0.9873021

00:24:51.390 --> 00:24:52.750 had about ninety cells per

NOTE Confidence: 0.9873021

00:24:52.750 --> 00:24:54.350 guide RNA. And so we

NOTE Confidence: 0.9873021

00:24:54.350 --> 00:24:55.710 have, you know, a grand

NOTE Confidence: 0.9873021

00:24:55.710 --> 00:24:57.010 total of of

NOTE Confidence: 0.98641783

00:24:57.335 --> 00:24:59.575 twenty thousand gene expression points

NOTE Confidence: 0.98641783

00:24:59.575 --> 00:25:00.455 for every single one of

NOTE Confidence: 0.98641783

00:25:00.455 --> 00:25:01.895 these single cells. So you

NOTE Confidence: 0.98641783

00:25:01.895 --> 00:25:03.335 see we created this matrix

NOTE Confidence: 0.98641783

00:25:03.335 --> 00:25:04.555 at the top right corner

NOTE Confidence: 0.97494704

00:25:05.255 --> 00:25:06.775 of cells per genes. And

NOTE Confidence: 0.97494704

00:25:06.775 --> 00:25:08.055 at this point, we can't

NOTE Confidence: 0.97494704

00:25:08.055 --> 00:25:09.255 analyze this data with an

NOTE Confidence: 0.97494704

00:25:09.255 --> 00:25:10.775 Excel spreadsheet. Right? This is

NOTE Confidence: 0.97494704

00:25:10.775 --> 00:25:12.155 a huge amount of data

NOTE Confidence: 0.97494704

00:25:12.440 --> 00:25:13.320 for a huge amount of

NOTE Confidence: 0.97494704

00:25:13.320 --> 00:25:14.280 genes. And so we had

NOTE Confidence: 0.97494704

00:25:14.280 --> 00:25:15.160 to think about how to

NOTE Confidence: 0.97494704

00:25:15.160 --> 00:25:16.119 analyze the data, and we

NOTE Confidence: 0.97494704

00:25:16.119 --> 00:25:17.240 went through many iterations. And

NOTE Confidence: 0.97494704

00:25:17.240 --> 00:25:18.440 with a great collaborator at

NOTE Confidence: 0.97494704

00:25:18.440 --> 00:25:19.660 Stanford, Jesse Engreits,

NOTE Confidence: 0.9708467

00:25:20.119 --> 00:25:21.720 we built a, we applied

NOTE Confidence: 0.9708467

00:25:21.720 --> 00:25:23.559 basically what's called topic modeling.

NOTE Confidence: 0.9708467

00:25:23.559 --> 00:25:24.859 And this was a algorithm

NOTE Confidence: 0.9708467

00:25:24.920 --> 00:25:26.055 that was developed by Twitter

NOTE Confidence: 0.9708467

00:25:26.375 --> 00:25:27.494 when they used to share,

NOTE Confidence: 0.9708467

00:25:27.735 --> 00:25:29.175 all their algorithms and computer

NOTE Confidence: 0.9708467

00:25:29.175 --> 00:25:31.575 science, pipelines. But if Twitter

NOTE Confidence: 0.9708467

00:25:31.575 --> 00:25:32.855 was gonna say that today,

NOTE Confidence: 0.9708467

00:25:32.855 --> 00:25:34.855 Yale University is trending, they

NOTE Confidence: 0.9708467

00:25:34.855 --> 00:25:35.895 don't just count the number

NOTE Confidence: 0.9708467

00:25:35.895 --> 00:25:37.415 of times someone mentions Yale

NOTE Confidence: 0.9708467

00:25:37.415 --> 00:25:39.175 University in tweets. They have

NOTE Confidence: 0.9708467

00:25:39.175 --> 00:25:39.994 a a topic

NOTE Confidence: 0.88992035

00:25:40.510 --> 00:25:42.210 of co expressed words

NOTE Confidence: 0.95197994

00:25:42.670 --> 00:25:44.429 with the word Yale. And

NOTE Confidence: 0.95197994

00:25:44.429 --> 00:25:46.190 that might be New Haven,

NOTE Confidence: 0.95197994

00:25:46.190 --> 00:25:47.549 that might be Connecticut, that

NOTE Confidence: 0.95197994

00:25:47.549 --> 00:25:48.750 might be Harvard, that might

NOTE Confidence: 0.95197994

00:25:48.750 --> 00:25:50.030 be, you know, Columbia, that

NOTE Confidence: 0.95197994

00:25:50.030 --> 00:25:51.230 might be, you know, oh

NOTE Confidence: 0.95197994

00:25:51.230 --> 00:25:52.429 oh, you know, Yale New

NOTE Confidence: 0.95197994

00:25:52.429 --> 00:25:54.130 Haven Hospital. That's that coexpress

NOTE Confidence: 0.95197994

00:25:54.350 --> 00:25:55.165 set, and and that's how

NOTE Confidence: 0.95197994

00:25:55.165 --> 00:25:56.285 they tell you what topics

NOTE Confidence: 0.95197994

00:25:56.285 --> 00:25:57.885 are trending. So we applied

NOTE Confidence: 0.95197994

00:25:57.885 --> 00:25:59.244 that same algorithm to our

NOTE Confidence: 0.95197994

00:25:59.244 --> 00:26:00.285 data. We wanted to look

NOTE Confidence: 0.95197994

00:26:00.285 --> 00:26:01.025 at coregulated

NOTE Confidence: 0.9584652

00:26:01.325 --> 00:26:02.065 gene networks.

NOTE Confidence: 0.9728391

00:26:02.685 --> 00:26:03.885 And the amount of data

NOTE Confidence: 0.9728391

00:26:03.885 --> 00:26:05.405 we had was incredible, and

NOTE Confidence: 0.9728391

00:26:05.405 --> 00:26:06.685 I could spend the next

NOTE Confidence: 0.9728391

00:26:06.685 --> 00:26:07.805 forty minutes, and I'd love

NOTE Confidence: 0.9728391

00:26:07.805 --> 00:26:09.500 to, going through each one

NOTE Confidence: 0.9728391

00:26:09.500 --> 00:26:10.859 of those discoveries that we

NOTE Confidence: 0.9728391

00:26:10.859 --> 00:26:12.380 made using this data, but

NOTE Confidence: 0.9728391

00:26:12.380 --> 00:26:13.580 I won't. I I I'll

NOTE Confidence: 0.9728391

00:26:13.580 --> 00:26:15.100 really resist. I'll just focus

NOTE Confidence: 0.9728391

00:26:15.100 --> 00:26:16.380 on the three kind of

NOTE Confidence: 0.9728391

00:26:16.380 --> 00:26:17.900 really clinically relevant and what

NOTE Confidence: 0.9728391

00:26:17.900 --> 00:26:18.859 I thought were the most

NOTE Confidence: 0.9728391

00:26:18.859 --> 00:26:19.359 interesting

NOTE Confidence: 0.988669

00:26:19.900 --> 00:26:21.020 stories that came from this

NOTE Confidence: 0.988669

00:26:21.020 --> 00:26:22.795 data. The first is that

NOTE Confidence: 0.988669

00:26:22.795 --> 00:26:24.175 we can find the regulators

NOTE Confidence: 0.988669

00:26:24.235 --> 00:26:25.915 and coregulated gene networks in

NOTE Confidence: 0.988669

00:26:25.915 --> 00:26:27.355 an unbiased way from this

NOTE Confidence: 0.988669

00:26:27.355 --> 00:26:28.175 sort of experiment.

NOTE Confidence: 0.9838024

00:26:28.795 --> 00:26:30.475 The second is that central

NOTE Confidence: 0.9838024

00:26:30.475 --> 00:26:32.475 genes for coronary disease are

NOTE Confidence: 0.9838024

00:26:32.475 --> 00:26:34.570 shared between multiple vascular diseases,

NOTE Confidence: 0.9838024

00:26:34.630 --> 00:26:35.510 and that's been sort of

NOTE Confidence: 0.9838024

00:26:35.510 --> 00:26:36.950 the motivation for my clinic

NOTE Confidence: 0.9838024

00:26:36.950 --> 00:26:37.670 now, and I'll get I'll

NOTE Confidence: 0.9838024

00:26:37.670 --> 00:26:39.109 get into that. Right? We

NOTE Confidence: 0.9838024

00:26:39.109 --> 00:26:40.390 often talk about ourselves as

NOTE Confidence: 0.9838024

00:26:40.390 --> 00:26:41.850 a cardiovascular division,

NOTE Confidence: 0.99499005

00:26:42.150 --> 00:26:43.190 but a lot of vascular

NOTE Confidence: 0.99499005

00:26:43.190 --> 00:26:44.570 patients see neurosurgeons

NOTE Confidence: 0.99243665

00:26:44.950 --> 00:26:46.484 for some reason. And so,

NOTE Confidence: 0.99243665

00:26:46.484 --> 00:26:47.684 you know, can we sort

NOTE Confidence: 0.99243665

00:26:47.684 --> 00:26:48.005 of,

NOTE Confidence: 0.96786964

00:26:48.565 --> 00:26:50.725 provide insights into other diseases

NOTE Confidence: 0.96786964

00:26:50.725 --> 00:26:51.845 that just aren't happen to

NOTE Confidence: 0.96786964

00:26:51.845 --> 00:26:53.145 be next to the heart?

NOTE Confidence: 0.9642114

00:26:53.605 --> 00:26:55.365 And then finally, I made

NOTE Confidence: 0.9642114

00:26:55.365 --> 00:26:55.865 a

NOTE Confidence: 0.7355464

00:26:56.244 --> 00:26:56.905 a a independent

NOTE Confidence: 0.97337174

00:26:57.365 --> 00:26:59.160 EC driven risk pathway

NOTE Confidence: 0.98501396

00:26:59.540 --> 00:27:01.300 to target with maybe precision

NOTE Confidence: 0.98501396

00:27:01.300 --> 00:27:02.500 therapies and see if it

NOTE Confidence: 0.98501396

00:27:02.500 --> 00:27:04.359 predicted risk in patient populations

NOTE Confidence: 0.98501396

00:27:04.580 --> 00:27:05.080 uniquely.

NOTE Confidence: 0.9945442

00:27:05.380 --> 00:27:06.180 And so those are the

NOTE Confidence: 0.9945442

00:27:06.180 --> 00:27:07.540 three stories I'll share with

NOTE Confidence: 0.9945442

00:27:07.540 --> 00:27:09.160 the last twenty minutes here.

NOTE Confidence: 0.9945442

00:27:09.380 --> 00:27:10.600 And so the first,

NOTE Confidence: 0.99185705

00:27:11.134 --> 00:27:12.335 is the just the raw

NOTE Confidence: 0.99185705

00:27:12.335 --> 00:27:13.615 data from our screen. So

NOTE Confidence: 0.99185705

00:27:13.615 --> 00:27:15.054 for a cardiology audience, I

NOTE Confidence: 0.99185705

00:27:15.054 --> 00:27:16.195 like to use this example.

NOTE Confidence: 0.9125202

00:27:16.494 --> 00:27:17.955 This is HMG coereoiductase.

NOTE Confidence: 0.9709623

00:27:18.335 --> 00:27:19.455 Right? The target of statins.

NOTE Confidence: 0.9709623

00:27:19.455 --> 00:27:20.254 So let's say you didn't

NOTE Confidence: 0.9709623

00:27:20.254 --> 00:27:21.634 know what this gene did.

NOTE Confidence: 0.9709623

00:27:21.855 --> 00:27:23.394 Even though I'm studying endothelial

NOTE Confidence: 0.9709623

00:27:23.534 --> 00:27:24.734 cells, this isn't even in

NOTE Confidence: 0.9709623

00:27:24.734 --> 00:27:25.315 the liver,

NOTE Confidence: 0.9827733

00:27:25.880 --> 00:27:27.000 our data would tell you

NOTE Confidence: 0.9827733

00:27:27.000 --> 00:27:27.960 that this is a major

NOTE Confidence: 0.9827733

00:27:27.960 --> 00:27:29.880 regulator of cholesterol biosynthesis. So

NOTE Confidence: 0.9827733

00:27:29.880 --> 00:27:31.000 in our data, you see

NOTE Confidence: 0.9827733

00:27:31.000 --> 00:27:31.960 that we had a hundred

NOTE Confidence: 0.9827733

00:27:31.960 --> 00:27:33.720 and sixty cells that got

NOTE Confidence: 0.9827733

00:27:33.720 --> 00:27:35.080 a CRISPR knockdown for the

NOTE Confidence: 0.9827733

00:27:35.080 --> 00:27:37.160 gene HMG cholera reductase, and

NOTE Confidence: 0.9827733

00:27:37.160 --> 00:27:38.440 we had six thousand cells

NOTE Confidence: 0.9827733

00:27:38.440 --> 00:27:39.525 that got a negative control

NOTE Confidence: 0.9827733

00:27:39.525 --> 00:27:40.244 guide. And so we got

NOTE Confidence: 0.9827733

00:27:40.244 --> 00:27:41.845 about fifty percent knockdown of

NOTE Confidence: 0.9827733

00:27:41.845 --> 00:27:43.365 that gene. Then when we

NOTE Confidence: 0.9827733

00:27:43.365 --> 00:27:44.805 look at the expression data,

NOTE Confidence: 0.9827733

00:27:44.805 --> 00:27:46.244 the effect of HMG co

NOTE Confidence: 0.9827733

00:27:46.244 --> 00:27:46.744 reductase

NOTE Confidence: 0.9344268

00:27:47.525 --> 00:27:48.025 knockdown,

NOTE Confidence: 0.9008009

00:27:48.405 --> 00:27:49.445 you see that there's up

NOTE Confidence: 0.9008009

00:27:49.445 --> 00:27:50.269 regulation of every gene in

NOTE Confidence: 0.9008009

00:27:50.269 --> 00:27:50.331 the cholesterol biosynthesis pathway. So,

NOTE Confidence: 0.9008009

00:27:50.331 --> 00:27:50.392 yes, HMG co reductase is

NOTE Confidence: 0.9008009

00:27:50.392 --> 00:27:50.905 a regulator

NOTE Confidence: 0.9560722

00:27:51.285 --> 00:27:53.460 of biosynthesis pathway. So, yes,

NOTE Confidence: 0.9560722

00:27:53.460 --> 00:27:54.980 HMG choroid ductase is a

NOTE Confidence: 0.9560722

00:27:54.980 --> 00:27:57.060 regulator of cholesterol biosynthesis. No

NOTE Confidence: 0.9560722

00:27:57.060 --> 00:27:58.100 surprise to anyone in this

NOTE Confidence: 0.9560722

00:27:58.100 --> 00:27:59.700 audience. And that was one

NOTE Confidence: 0.9560722

00:27:59.700 --> 00:28:01.220 of our topics. Right? You'll

NOTE Confidence: 0.9560722

00:28:01.220 --> 00:28:02.680 see here that topic nineteen

NOTE Confidence: 0.9560722

00:28:02.820 --> 00:28:03.940 kinda halfway down the left

NOTE Confidence: 0.9560722

00:28:03.940 --> 00:28:05.400 side of the the slide

NOTE Confidence: 0.96538734

00:28:05.700 --> 00:28:07.240 is the cholesterol biosynthesis

NOTE Confidence: 0.99324447

00:28:08.215 --> 00:28:09.575 pathway. In total, we had

NOTE Confidence: 0.99324447

00:28:09.575 --> 00:28:11.494 fifty of these coregulated networks

NOTE Confidence: 0.99324447

00:28:11.494 --> 00:28:12.855 that were identified from topic

NOTE Confidence: 0.99324447

00:28:12.855 --> 00:28:13.355 modeling.

NOTE Confidence: 0.98178726

00:28:14.215 --> 00:28:15.414 Thirty seven of them have

NOTE Confidence: 0.98178726

00:28:15.414 --> 00:28:16.615 nothing to do with endothelial

NOTE Confidence: 0.98178726

00:28:16.615 --> 00:28:17.914 cells. They're sort of ubiquitous

NOTE Confidence: 0.98178726

00:28:18.054 --> 00:28:19.095 pathways that would have been

NOTE Confidence: 0.98178726

00:28:19.095 --> 00:28:20.100 found in any cell type.

NOTE Confidence: 0.98178726

00:28:20.179 --> 00:28:22.340 Type. Right? Ribosomal biology or

NOTE Confidence: 0.98178726

00:28:22.340 --> 00:28:23.400 cell cycle control.

NOTE Confidence: 0.95872676

00:28:23.940 --> 00:28:25.140 But in the box are

NOTE Confidence: 0.95872676

00:28:25.140 --> 00:28:27.700 thirteen endothelial cell specific pathways

NOTE Confidence: 0.95872676

00:28:27.700 --> 00:28:28.660 that I'm sure are near

NOTE Confidence: 0.95872676

00:28:28.660 --> 00:28:29.460 and dear to someone like

NOTE Confidence: 0.95872676

00:28:29.460 --> 00:28:30.820 Dan Greif's heart here, like

NOTE Confidence: 0.95872676

00:28:30.820 --> 00:28:31.320 EndoMT

NOTE Confidence: 0.9677618

00:28:31.859 --> 00:28:34.924 or, angiogenesis here. And these

NOTE Confidence: 0.9677618

00:28:34.924 --> 00:28:36.524 pathways, I think, are the

NOTE Confidence: 0.9677618

00:28:36.524 --> 00:28:38.684 disease relevant pathways. So we

NOTE Confidence: 0.9677618

00:28:38.684 --> 00:28:39.565 wanted to see which of

NOTE Confidence: 0.9677618

00:28:39.565 --> 00:28:41.505 these showed enrichment for GWAS

NOTE Confidence: 0.9677618

00:28:41.565 --> 00:28:43.164 risk. And, again, we applied,

NOTE Confidence: 0.9677618

00:28:43.325 --> 00:28:44.044 you know, sort of a

NOTE Confidence: 0.9677618

00:28:44.044 --> 00:28:45.485 series of statistical tests to

NOTE Confidence: 0.9677618

00:28:45.485 --> 00:28:46.784 see which of these pathways

NOTE Confidence: 0.96981865

00:28:47.350 --> 00:28:48.870 were enriched for GWAS risk

NOTE Confidence: 0.96981865

00:28:48.870 --> 00:28:49.370 loci.

NOTE Confidence: 0.99326044

00:28:49.990 --> 00:28:52.009 And every test we applied,

NOTE Confidence: 0.99326044

00:28:52.070 --> 00:28:53.850 it was basically one pathway

NOTE Confidence: 0.99326044

00:28:53.909 --> 00:28:54.870 rose to the top, and

NOTE Confidence: 0.99326044

00:28:54.870 --> 00:28:55.750 that's what I'm showing you

NOTE Confidence: 0.99326044

00:28:55.750 --> 00:28:57.190 here. And I didn't know

NOTE Confidence: 0.99326044

00:28:57.190 --> 00:28:58.149 the name of this pathway

NOTE Confidence: 0.99326044

00:28:58.149 --> 00:28:59.110 when we found it from

NOTE Confidence: 0.99326044

00:28:59.110 --> 00:29:00.149 our data, but it's called

NOTE Confidence: 0.99326044

00:29:00.149 --> 00:29:00.809 the CCM

NOTE Confidence: 0.94048387

00:29:01.475 --> 00:29:03.495 pathway, the cerebral cavernous malformation

NOTE Confidence: 0.94048387

00:29:03.555 --> 00:29:04.455 complex pathway.

NOTE Confidence: 0.9477498

00:29:05.155 --> 00:29:06.755 It's named for Mendelian disorder

NOTE Confidence: 0.9477498

00:29:06.755 --> 00:29:07.715 that I'm gonna talk about

NOTE Confidence: 0.9477498

00:29:07.715 --> 00:29:08.455 in a second.

NOTE Confidence: 0.9758545

00:29:08.915 --> 00:29:10.275 But you'll see that there's

NOTE Confidence: 0.9758545

00:29:10.275 --> 00:29:12.115 genes upstream of KLF two

NOTE Confidence: 0.9758545

00:29:12.115 --> 00:29:13.500 and genes downstream of

NOTE Confidence: 0.9868633

00:29:14.300 --> 00:29:15.820 two. And in total, forty

NOTE Confidence: 0.9868633

00:29:15.820 --> 00:29:17.500 one of the GWAS hits

NOTE Confidence: 0.9868633

00:29:17.500 --> 00:29:19.260 for coronary disease are in

NOTE Confidence: 0.9868633

00:29:19.260 --> 00:29:20.000 this pathway.

NOTE Confidence: 0.9847089

00:29:20.380 --> 00:29:21.820 So forty seven of the

NOTE Confidence: 0.9847089

00:29:21.820 --> 00:29:23.660 GWAS hits for coronary disease

NOTE Confidence: 0.9847089

00:29:23.660 --> 00:29:25.100 are in the LDL pathway.

NOTE Confidence: 0.9847089

00:29:25.100 --> 00:29:26.655 Right? Something that we unquestionably

NOTE Confidence: 0.9847089

00:29:26.955 --> 00:29:28.875 say causes coronary disease. And

NOTE Confidence: 0.9847089

00:29:28.875 --> 00:29:30.235 here, just about the same

NOTE Confidence: 0.9847089

00:29:30.235 --> 00:29:31.935 number are in this CCM

NOTE Confidence: 0.9847089

00:29:32.075 --> 00:29:32.575 pathway.

NOTE Confidence: 0.95736206

00:29:33.435 --> 00:29:36.155 And it's regulated by three

NOTE Confidence: 0.95736206

00:29:36.155 --> 00:29:37.115 genes at the center of

NOTE Confidence: 0.95736206

00:29:37.115 --> 00:29:38.310 the CCM complex.

NOTE Confidence: 0.98075545

00:29:38.950 --> 00:29:40.650 And genes that are upstream

NOTE Confidence: 0.98075545

00:29:40.710 --> 00:29:41.990 of KLF two, so in

NOTE Confidence: 0.98075545

00:29:41.990 --> 00:29:42.870 the the top part of

NOTE Confidence: 0.98075545

00:29:42.870 --> 00:29:43.830 the slide, when you knock

NOTE Confidence: 0.98075545

00:29:43.830 --> 00:29:45.350 them down, they have a

NOTE Confidence: 0.98075545

00:29:45.350 --> 00:29:47.290 protective effect on coronary disease,

NOTE Confidence: 0.98075545

00:29:47.510 --> 00:29:49.430 and genes downstream of KLF

NOTE Confidence: 0.98075545

00:29:49.430 --> 00:29:50.230 two, when you knock them

NOTE Confidence: 0.98075545

00:29:50.230 --> 00:29:51.465 down, have the opposite effect.

NOTE Confidence: 0.98075545

00:29:51.465 --> 00:29:52.345 So this is, like, you

NOTE Confidence: 0.98075545

00:29:52.345 --> 00:29:53.225 know, kind of from our

NOTE Confidence: 0.98075545

00:29:53.225 --> 00:29:54.184 data, you're able to sort

NOTE Confidence: 0.98075545

00:29:54.184 --> 00:29:55.544 of see the directionality of

NOTE Confidence: 0.98075545

00:29:55.544 --> 00:29:56.765 the effect on disease.

NOTE Confidence: 0.99740833

00:29:57.225 --> 00:29:58.184 So then I had to

NOTE Confidence: 0.99740833

00:29:58.184 --> 00:29:59.145 read a lot of papers

NOTE Confidence: 0.99740833

00:29:59.145 --> 00:30:00.205 that came from Yale,

NOTE Confidence: 0.9801574

00:30:01.145 --> 00:30:02.424 on what is this pathway.

NOTE Confidence: 0.9801574

00:30:02.424 --> 00:30:03.304 And it turns out it

NOTE Confidence: 0.9801574

00:30:03.304 --> 00:30:04.904 was sort of discovered because

NOTE Confidence: 0.9801574

00:30:04.904 --> 00:30:06.050 when you have loss of

NOTE Confidence: 0.9801574

00:30:06.050 --> 00:30:07.830 function mutations in these genes,

NOTE Confidence: 0.9801574

00:30:07.970 --> 00:30:09.650 it drives a cerebral vascular

NOTE Confidence: 0.9801574

00:30:09.650 --> 00:30:11.670 disease called cerebral cavernous malformations.

NOTE Confidence: 0.9761765

00:30:12.130 --> 00:30:13.490 Extremely rare. One in a

NOTE Confidence: 0.9761765

00:30:13.490 --> 00:30:14.610 hundred thousand, one in five

NOTE Confidence: 0.9761765

00:30:14.610 --> 00:30:16.230 hundred thousand patients have it.

NOTE Confidence: 0.9761765

00:30:16.370 --> 00:30:17.570 But when they have large

NOTE Confidence: 0.9761765

00:30:17.570 --> 00:30:19.170 deletions in the CCM two

NOTE Confidence: 0.9761765

00:30:19.170 --> 00:30:20.865 gene, for example, they get

NOTE Confidence: 0.9761765

00:30:20.865 --> 00:30:23.105 these, these black spots on

NOTE Confidence: 0.9761765

00:30:23.105 --> 00:30:24.625 their MRI, which are blood

NOTE Confidence: 0.9761765

00:30:24.625 --> 00:30:27.045 blisters essentially. They're venous malformations.

NOTE Confidence: 0.9761765

00:30:27.265 --> 00:30:28.165 They're outpouchings

NOTE Confidence: 0.9897532

00:30:28.465 --> 00:30:30.165 of venous endothelial cells.

NOTE Confidence: 0.99183315

00:30:30.545 --> 00:30:32.225 But what we're finding from

NOTE Confidence: 0.99183315

00:30:32.225 --> 00:30:34.170 GWAS is that common mutations

NOTE Confidence: 0.99183315

00:30:34.390 --> 00:30:35.610 in the same pathway

NOTE Confidence: 0.99483144

00:30:35.990 --> 00:30:38.150 are somehow protective. So eight

NOTE Confidence: 0.99483144

00:30:38.150 --> 00:30:39.210 percent of Europeans

NOTE Confidence: 0.998878

00:30:39.910 --> 00:30:41.290 have protective mutations

NOTE Confidence: 0.9820625

00:30:42.150 --> 00:30:43.750 in this pathway that lower

NOTE Confidence: 0.9820625

00:30:43.750 --> 00:30:45.290 their risk of coronary disease.

NOTE Confidence: 0.97763073

00:30:45.965 --> 00:30:46.925 And so we weren't sure,

NOTE Confidence: 0.97763073

00:30:46.925 --> 00:30:47.485 you know, do we have

NOTE Confidence: 0.97763073

00:30:47.485 --> 00:30:49.005 the directionality wrong? Is this

NOTE Confidence: 0.97763073

00:30:49.005 --> 00:30:50.365 really real? So we may

NOTE Confidence: 0.97763073

00:30:50.365 --> 00:30:51.725 knock out mice. Right? Something

NOTE Confidence: 0.97763073

00:30:51.725 --> 00:30:52.685 that I hadn't really done

NOTE Confidence: 0.97763073

00:30:52.685 --> 00:30:53.665 a lot of before,

NOTE Confidence: 0.9731705

00:30:54.045 --> 00:30:55.405 but we we we felt

NOTE Confidence: 0.9731705

00:30:55.405 --> 00:30:56.445 like, you know, I'd, sort

NOTE Confidence: 0.9731705

00:30:56.445 --> 00:30:57.885 of resisted going into, like,

NOTE Confidence: 0.9731705

00:30:57.885 --> 00:30:59.405 a biologic model system, but

NOTE Confidence: 0.9731705

00:30:59.405 --> 00:31:00.205 we really had to do

NOTE Confidence: 0.9731705

00:31:00.205 --> 00:31:01.260 it. And you see that

NOTE Confidence: 0.9731705

00:31:01.260 --> 00:31:02.060 here when you take a

NOTE Confidence: 0.9731705

00:31:02.060 --> 00:31:04.000 heterozygous CCM mouse, a homozygous

NOTE Confidence: 0.9731705

00:31:04.060 --> 00:31:05.340 knockout is lethal. Right? They

NOTE Confidence: 0.9731705

00:31:05.340 --> 00:31:06.780 don't make a vascular system.

NOTE Confidence: 0.9731705

00:31:06.780 --> 00:31:08.060 It's very involved in vascular

NOTE Confidence: 0.9731705

00:31:08.060 --> 00:31:09.980 development. But in heterozygous mice,

NOTE Confidence: 0.9731705

00:31:09.980 --> 00:31:11.260 in both male and female

NOTE Confidence: 0.9731705

00:31:11.260 --> 00:31:12.540 mice, there's a trend toward

NOTE Confidence: 0.9731705

00:31:12.540 --> 00:31:13.040 lower,

NOTE Confidence: 0.8728283

00:31:13.500 --> 00:31:14.000 atherosclerosis.

NOTE Confidence: 0.97974694

00:31:14.615 --> 00:31:15.815 And it's significant in the

NOTE Confidence: 0.97974694

00:31:15.815 --> 00:31:17.015 female mice who get more

NOTE Confidence: 0.97974694

00:31:17.015 --> 00:31:18.535 athero in general in this

NOTE Confidence: 0.97974694

00:31:18.535 --> 00:31:19.035 model.

NOTE Confidence: 0.95489234

00:31:20.055 --> 00:31:21.975 And then what was really

NOTE Confidence: 0.95489234

00:31:21.975 --> 00:31:23.095 interesting to us is we

NOTE Confidence: 0.95489234

00:31:23.095 --> 00:31:24.475 then looked at, like, well,

NOTE Confidence: 0.95489234

00:31:24.615 --> 00:31:25.895 this pathway hit on the

NOTE Confidence: 0.95489234

00:31:25.895 --> 00:31:27.115 left had been described

NOTE Confidence: 0.93232805

00:31:27.415 --> 00:31:28.235 in the literature.

NOTE Confidence: 0.94911116

00:31:28.560 --> 00:31:29.760 But could we find new

NOTE Confidence: 0.94911116

00:31:29.760 --> 00:31:31.200 regulators of this pathway? And

NOTE Confidence: 0.94911116

00:31:31.200 --> 00:31:32.420 were those new regulators

NOTE Confidence: 0.9934909

00:31:32.960 --> 00:31:34.800 also associated with coronary artery

NOTE Confidence: 0.9934909

00:31:34.800 --> 00:31:36.160 disease risk? And so what

NOTE Confidence: 0.9934909

00:31:36.160 --> 00:31:37.360 I'm showing you is that

NOTE Confidence: 0.9934909

00:31:37.360 --> 00:31:38.560 these are the forty one

NOTE Confidence: 0.9934909

00:31:38.560 --> 00:31:39.060 genes,

NOTE Confidence: 0.98031247

00:31:39.600 --> 00:31:41.680 that are, GWAS loci. These

NOTE Confidence: 0.98031247

00:31:41.680 --> 00:31:43.875 are CAD, GWAS loci. These

NOTE Confidence: 0.98031247

00:31:43.875 --> 00:31:44.595 are this is part of

NOTE Confidence: 0.98031247

00:31:44.595 --> 00:31:46.195 that GWAS pathway that we

NOTE Confidence: 0.98031247

00:31:46.195 --> 00:31:47.895 think are endothelial cell acting.

NOTE Confidence: 0.98031247

00:31:48.035 --> 00:31:49.075 And when you knock down

NOTE Confidence: 0.98031247

00:31:49.075 --> 00:31:50.355 CCM two, it has this

NOTE Confidence: 0.98031247

00:31:50.355 --> 00:31:51.875 sort of regulatory effect on

NOTE Confidence: 0.98031247

00:31:51.875 --> 00:31:52.915 all forty one of those

NOTE Confidence: 0.98031247

00:31:52.915 --> 00:31:54.115 genes. But there was a

NOTE Confidence: 0.98031247

00:31:54.115 --> 00:31:55.235 second gene that even had

NOTE Confidence: 0.98031247

00:31:55.235 --> 00:31:56.275 a bigger effect on these

NOTE Confidence: 0.98031247

00:31:56.275 --> 00:31:57.495 genes. It was called TLNRD

NOTE Confidence: 0.98031247

00:31:57.715 --> 00:31:58.890 one, and there were no

NOTE Confidence: 0.98031247

00:31:58.890 --> 00:32:00.010 papers on this gene. Right?

NOTE Confidence: 0.98031247

00:32:00.010 --> 00:32:01.050 So you you look it

NOTE Confidence: 0.98031247

00:32:01.050 --> 00:32:02.010 up in PubMed, not a

NOTE Confidence: 0.98031247

00:32:02.010 --> 00:32:02.830 single paper.

NOTE Confidence: 0.9458126

00:32:04.410 --> 00:32:05.770 And what we found is

NOTE Confidence: 0.9458126

00:32:05.770 --> 00:32:07.290 that this gene what you

NOTE Confidence: 0.9458126

00:32:07.290 --> 00:32:08.010 see on the left is

NOTE Confidence: 0.9458126

00:32:08.010 --> 00:32:09.550 that it's the strongest regulator

NOTE Confidence: 0.9458126

00:32:09.610 --> 00:32:11.310 of the CAD associated pathways.

NOTE Confidence: 0.96847326

00:32:11.625 --> 00:32:12.905 CCM two was number two,

NOTE Confidence: 0.96847326

00:32:12.905 --> 00:32:14.585 and HMG choroid ductase was

NOTE Confidence: 0.96847326

00:32:14.585 --> 00:32:16.105 number five. And it also

NOTE Confidence: 0.96847326

00:32:16.105 --> 00:32:17.705 showed the greatest correlation with

NOTE Confidence: 0.96847326

00:32:17.705 --> 00:32:19.545 CCM two knockdown. And all

NOTE Confidence: 0.96847326

00:32:19.545 --> 00:32:20.665 the other genes in black

NOTE Confidence: 0.96847326

00:32:20.665 --> 00:32:22.765 on this other, waterfall plot,

NOTE Confidence: 0.96847326

00:32:22.905 --> 00:32:24.425 all those other genes are

NOTE Confidence: 0.96847326

00:32:24.425 --> 00:32:25.785 known members of the CCM

NOTE Confidence: 0.96847326

00:32:25.785 --> 00:32:26.825 complex. T one r d

NOTE Confidence: 0.96847326

00:32:26.825 --> 00:32:27.690 one was sort of never

NOTE Confidence: 0.96847326

00:32:27.690 --> 00:32:28.190 discovered

NOTE Confidence: 0.94702286

00:32:28.490 --> 00:32:29.770 despite, you know, twenty years

NOTE Confidence: 0.94702286

00:32:29.770 --> 00:32:30.570 of research on t one

NOTE Confidence: 0.94702286

00:32:30.570 --> 00:32:31.850 r d one. So we

NOTE Confidence: 0.94702286

00:32:31.850 --> 00:32:33.130 then, you know, now getting

NOTE Confidence: 0.94702286

00:32:33.130 --> 00:32:34.570 into the basic biochemistry, we

NOTE Confidence: 0.94702286

00:32:34.570 --> 00:32:35.770 went to alpha fold. Right?

NOTE Confidence: 0.94702286

00:32:35.770 --> 00:32:36.890 Alpha fold had just come

NOTE Confidence: 0.94702286

00:32:36.890 --> 00:32:38.270 out and you could,

NOTE Confidence: 0.98950183

00:32:38.730 --> 00:32:40.169 make a crystal structure of

NOTE Confidence: 0.98950183

00:32:40.169 --> 00:32:41.385 a complex of proteins.

NOTE Confidence: 0.9093817

00:32:41.865 --> 00:32:42.905 And we we put two

NOTE Confidence: 0.9093817

00:32:42.905 --> 00:32:43.705 one r d one in,

NOTE Confidence: 0.9093817

00:32:43.705 --> 00:32:45.065 which is the orange protein

NOTE Confidence: 0.9093817

00:32:45.065 --> 00:32:46.585 at the bottom, and CCM

NOTE Confidence: 0.9093817

00:32:46.585 --> 00:32:47.805 two is the green protein.

NOTE Confidence: 0.9093817

00:32:47.865 --> 00:32:49.545 An alpha fold predicted that

NOTE Confidence: 0.9093817

00:32:49.545 --> 00:32:50.345 two one r d one

NOTE Confidence: 0.9093817

00:32:50.345 --> 00:32:51.785 would directly bind to this

NOTE Confidence: 0.9093817

00:32:51.785 --> 00:32:52.765 complex. So,

NOTE Confidence: 0.97511315

00:32:53.145 --> 00:32:54.360 and what what you see

NOTE Confidence: 0.97511315

00:32:54.360 --> 00:32:55.080 on the left is that

NOTE Confidence: 0.97511315

00:32:55.080 --> 00:32:56.440 it it was alpha fold

NOTE Confidence: 0.97511315

00:32:56.440 --> 00:32:57.660 was correctly predicting

NOTE Confidence: 0.8469785

00:32:58.040 --> 00:32:59.480 the CCM two crit one

NOTE Confidence: 0.8469785

00:32:59.480 --> 00:32:59.980 interaction,

NOTE Confidence: 0.9851282

00:33:00.280 --> 00:33:01.560 which is a known interaction

NOTE Confidence: 0.9851282

00:33:01.560 --> 00:33:02.920 for CCM two, and then

NOTE Confidence: 0.9851282

00:33:02.920 --> 00:33:04.380 we found this novel interaction.

NOTE Confidence: 0.9851282

00:33:04.600 --> 00:33:05.800 And then we confirmed it

NOTE Confidence: 0.9851282

00:33:05.800 --> 00:33:06.460 with immunoprecipitation

NOTE Confidence: 0.9872424

00:33:07.160 --> 00:33:08.360 experiments in this bottom right

NOTE Confidence: 0.9872424

00:33:08.360 --> 00:33:08.955 hand corner.

NOTE Confidence: 0.9171183

00:33:10.554 --> 00:33:11.755 And that's the only Western

NOTE Confidence: 0.9171183

00:33:11.755 --> 00:33:12.794 blot I will show during

NOTE Confidence: 0.9171183

00:33:12.794 --> 00:33:13.855 the rest of this talk.

NOTE Confidence: 0.9878475

00:33:15.995 --> 00:33:17.595 But from a functional biology

NOTE Confidence: 0.9878475

00:33:17.595 --> 00:33:18.875 standpoint, you know, we we

NOTE Confidence: 0.9878475

00:33:18.875 --> 00:33:20.475 now find this physical interaction

NOTE Confidence: 0.9878475

00:33:20.475 --> 00:33:21.960 between these two proteins, and

NOTE Confidence: 0.9878475

00:33:21.960 --> 00:33:23.080 we're seeing that they both

NOTE Confidence: 0.9878475

00:33:23.080 --> 00:33:24.760 have similar effects on how

NOTE Confidence: 0.9878475

00:33:24.760 --> 00:33:26.920 endothelial cells behave. So in

NOTE Confidence: 0.9878475

00:33:26.920 --> 00:33:28.040 the middle panel here, you

NOTE Confidence: 0.9878475

00:33:28.040 --> 00:33:28.840 see that when you put

NOTE Confidence: 0.9878475

00:33:28.840 --> 00:33:31.080 flow on endothelial cells, control

NOTE Confidence: 0.9878475

00:33:31.080 --> 00:33:32.440 endothelial cells, they all align

NOTE Confidence: 0.9878475

00:33:32.440 --> 00:33:33.800 in the same direction. They

NOTE Confidence: 0.9878475

00:33:33.800 --> 00:33:34.840 they develop this sort of

NOTE Confidence: 0.9878475

00:33:34.840 --> 00:33:35.900 protective phenotype.

NOTE Confidence: 0.96489173

00:33:36.205 --> 00:33:38.205 Those are happier quiescent endothelial

NOTE Confidence: 0.96489173

00:33:38.205 --> 00:33:39.405 cells when they're aligned to

NOTE Confidence: 0.96489173

00:33:39.405 --> 00:33:40.605 the direction of flow, and

NOTE Confidence: 0.96489173

00:33:40.605 --> 00:33:41.565 this is worked on by

NOTE Confidence: 0.96489173

00:33:41.565 --> 00:33:43.025 Martin Schwartz here at Yale.

NOTE Confidence: 0.9723637

00:33:43.325 --> 00:33:44.285 But when we knock out

NOTE Confidence: 0.9723637

00:33:44.285 --> 00:33:45.325 these two genes, they sort

NOTE Confidence: 0.9723637

00:33:45.325 --> 00:33:46.445 of have this similar effect.

NOTE Confidence: 0.9723637

00:33:46.445 --> 00:33:47.965 They cause this endothelial cell

NOTE Confidence: 0.9723637

00:33:47.965 --> 00:33:48.465 disarray,

NOTE Confidence: 0.98159695

00:33:49.540 --> 00:33:50.360 and they cause these accentuated

NOTE Confidence: 0.98159695

00:33:50.580 --> 00:33:52.100 stress fibers in the endothelial

NOTE Confidence: 0.98159695

00:33:52.100 --> 00:33:53.620 cells, but knockdown of these

NOTE Confidence: 0.98159695

00:33:53.620 --> 00:33:54.600 genes is protective.

NOTE Confidence: 0.992564

00:33:55.380 --> 00:33:56.500 So we don't know why

NOTE Confidence: 0.992564

00:33:56.500 --> 00:33:57.380 that is, but when we

NOTE Confidence: 0.992564

00:33:57.380 --> 00:33:59.240 look at barrier function, knockdown

NOTE Confidence: 0.992564

00:33:59.300 --> 00:34:00.980 results in increased barrier function

NOTE Confidence: 0.992564

00:34:00.980 --> 00:34:02.745 in these endothelial cells. So

NOTE Confidence: 0.992564

00:34:02.745 --> 00:34:03.865 what we think is happening

NOTE Confidence: 0.992564

00:34:03.865 --> 00:34:05.065 is that these cells are

NOTE Confidence: 0.992564

00:34:05.065 --> 00:34:06.205 resistant to flow,

NOTE Confidence: 0.9677825

00:34:06.585 --> 00:34:08.425 which normally is bad. Right?

NOTE Confidence: 0.9677825

00:34:08.425 --> 00:34:09.864 Responding to flow is good.

NOTE Confidence: 0.9677825

00:34:09.864 --> 00:34:11.545 When you exercise, the reason

NOTE Confidence: 0.9677825

00:34:11.545 --> 00:34:12.285 you vasodilate

NOTE Confidence: 0.9933133

00:34:12.665 --> 00:34:14.265 after exercise is you've raised

NOTE Confidence: 0.9933133

00:34:14.265 --> 00:34:15.510 your blood vascular

NOTE Confidence: 0.96975607

00:34:15.970 --> 00:34:17.170 cells, and then you you

NOTE Confidence: 0.96975607

00:34:17.170 --> 00:34:19.489 develop you express nitric oxide

NOTE Confidence: 0.96975607

00:34:19.489 --> 00:34:21.170 causing vasodilation. And I always

NOTE Confidence: 0.96975607

00:34:21.170 --> 00:34:22.050 like to think that, like,

NOTE Confidence: 0.96975607

00:34:22.050 --> 00:34:23.190 you've hit a reasonable,

NOTE Confidence: 0.99689186

00:34:23.570 --> 00:34:24.770 amount of exercise when you

NOTE Confidence: 0.99689186

00:34:24.770 --> 00:34:25.590 see that vasodilation.

NOTE Confidence: 0.9699702

00:34:26.450 --> 00:34:28.050 As people have hypertension for

NOTE Confidence: 0.9699702

00:34:28.050 --> 00:34:29.410 fifty years, they lose that

NOTE Confidence: 0.9699702

00:34:29.410 --> 00:34:31.505 response. So people who chronically

NOTE Confidence: 0.9699702

00:34:31.565 --> 00:34:32.065 hypertensive

NOTE Confidence: 0.9529866

00:34:32.765 --> 00:34:34.864 no longer vasodilate to exercise,

NOTE Confidence: 0.9978365

00:34:35.565 --> 00:34:36.525 and so they lose that

NOTE Confidence: 0.9978365

00:34:36.525 --> 00:34:38.065 protective endothelial effect.

NOTE Confidence: 0.9994818

00:34:38.525 --> 00:34:39.724 But if they have these

NOTE Confidence: 0.9994818

00:34:39.724 --> 00:34:41.984 mutations in their endothelial cells,

NOTE Confidence: 0.99418944

00:34:42.420 --> 00:34:44.020 they are resistant to flow.

NOTE Confidence: 0.99418944

00:34:44.020 --> 00:34:45.460 So they they might not

NOTE Confidence: 0.99418944

00:34:45.460 --> 00:34:46.900 vasodilate as much when they're

NOTE Confidence: 0.99418944

00:34:46.900 --> 00:34:48.579 younger, but they also don't

NOTE Confidence: 0.99418944

00:34:48.579 --> 00:34:50.040 lose the vasodilatory

NOTE Confidence: 0.99940675

00:34:50.420 --> 00:34:51.540 capacity that they have when

NOTE Confidence: 0.99940675

00:34:51.540 --> 00:34:52.839 they've been exposed to hypertension

NOTE Confidence: 0.99940675

00:34:52.980 --> 00:34:53.960 for fifty years.

NOTE Confidence: 0.98453295

00:34:54.305 --> 00:34:55.265 And so that's sort of

NOTE Confidence: 0.98453295

00:34:55.265 --> 00:34:56.945 our working hypothesis of the

NOTE Confidence: 0.98453295

00:34:56.945 --> 00:34:58.225 mechanism is that most of

NOTE Confidence: 0.98453295

00:34:58.225 --> 00:34:59.425 us in this room have

NOTE Confidence: 0.98453295

00:34:59.425 --> 00:34:59.925 atherosclerotic

NOTE Confidence: 0.96387947

00:35:00.305 --> 00:35:02.225 endothelium. Right? We're prone to

NOTE Confidence: 0.96387947

00:35:02.225 --> 00:35:03.265 all the bad things that

NOTE Confidence: 0.96387947

00:35:03.265 --> 00:35:05.205 happen in our endothelial cells,

NOTE Confidence: 0.9664695

00:35:05.505 --> 00:35:06.625 but a few of us

NOTE Confidence: 0.9664695

00:35:06.625 --> 00:35:08.245 have these genetically atheroprotective

NOTE Confidence: 0.966927

00:35:08.625 --> 00:35:10.090 endothelial cells. Endothelial cells. We

NOTE Confidence: 0.966927

00:35:10.090 --> 00:35:11.530 have these common variants in

NOTE Confidence: 0.966927

00:35:11.530 --> 00:35:13.130 these two genes that then

NOTE Confidence: 0.966927

00:35:13.130 --> 00:35:14.810 regulate forty one other risk

NOTE Confidence: 0.966927

00:35:14.810 --> 00:35:16.250 genes, and we have those

NOTE Confidence: 0.966927

00:35:16.250 --> 00:35:18.430 people have decreased vascular inflammation,

NOTE Confidence: 0.9703461

00:35:19.050 --> 00:35:21.310 increased nitric oxide production regardless

NOTE Confidence: 0.9703461

00:35:21.369 --> 00:35:22.730 of the flow conditions their

NOTE Confidence: 0.9703461

00:35:22.730 --> 00:35:24.125 cells are in. And so

NOTE Confidence: 0.9703461

00:35:24.125 --> 00:35:25.085 that, you know, that's a

NOTE Confidence: 0.9703461

00:35:25.085 --> 00:35:26.125 a mechanism that we don't

NOTE Confidence: 0.9703461

00:35:26.125 --> 00:35:26.625 target.

NOTE Confidence: 0.95673573

00:35:27.405 --> 00:35:28.925 You know you know, could

NOTE Confidence: 0.95673573

00:35:28.925 --> 00:35:30.204 we make drugs that sort

NOTE Confidence: 0.95673573

00:35:30.204 --> 00:35:31.405 of mimic the effect of

NOTE Confidence: 0.95673573

00:35:31.405 --> 00:35:31.905 exercise

NOTE Confidence: 0.99515676

00:35:32.364 --> 00:35:33.185 in the endothelium?

NOTE Confidence: 0.9891998

00:35:34.204 --> 00:35:35.484 Yes. And that's something that

NOTE Confidence: 0.9891998

00:35:35.484 --> 00:35:36.605 drug companies have tried to

NOTE Confidence: 0.9891998

00:35:36.605 --> 00:35:37.724 do, but, you know, maybe

NOTE Confidence: 0.9891998

00:35:37.724 --> 00:35:39.400 with human genetics, we can

NOTE Confidence: 0.9891998

00:35:39.400 --> 00:35:41.340 find the true nodal biology

NOTE Confidence: 0.9995983

00:35:41.719 --> 00:35:43.100 regulators of that pathway.

NOTE Confidence: 0.98791474

00:35:43.800 --> 00:35:45.480 So so from that, I

NOTE Confidence: 0.98791474

00:35:45.480 --> 00:35:46.840 wanna shift into what I

NOTE Confidence: 0.98791474

00:35:46.840 --> 00:35:48.200 sort of started the the

NOTE Confidence: 0.98791474

00:35:48.200 --> 00:35:49.260 talk on, which is

NOTE Confidence: 0.985423

00:35:49.640 --> 00:35:51.880 endothelial cell risk scores. And

NOTE Confidence: 0.985423

00:35:51.880 --> 00:35:53.480 can we identify a new

NOTE Confidence: 0.985423

00:35:53.480 --> 00:35:55.605 risk pathway from this data?

NOTE Confidence: 0.985423

00:35:55.605 --> 00:35:56.805 One of the criticisms of

NOTE Confidence: 0.985423

00:35:56.805 --> 00:35:57.864 GWAS is that

NOTE Confidence: 0.8662648

00:35:58.165 --> 00:35:58.965 you you just sort of

NOTE Confidence: 0.8662648

00:35:58.965 --> 00:35:59.445 find an un,

NOTE Confidence: 0.69799036

00:36:01.045 --> 00:36:01.545 unassociated

NOTE Confidence: 0.99124163

00:36:01.925 --> 00:36:03.045 list of genes. Right? They

NOTE Confidence: 0.99124163

00:36:03.045 --> 00:36:03.925 have nothing to do with

NOTE Confidence: 0.99124163

00:36:03.925 --> 00:36:04.585 each other.

NOTE Confidence: 0.9869861

00:36:05.125 --> 00:36:06.005 And if you did it

NOTE Confidence: 0.9869861

00:36:06.005 --> 00:36:07.125 for every disease, so the

NOTE Confidence: 0.9869861

00:36:07.125 --> 00:36:08.725 GWAS hits for schizophrenia and

NOTE Confidence: 0.9869861

00:36:08.725 --> 00:36:09.925 the GWAS hits for coronary

NOTE Confidence: 0.9869861

00:36:09.925 --> 00:36:11.680 disease overlap for some reason.

NOTE Confidence: 0.9869861

00:36:11.739 --> 00:36:12.700 So does that mean we're

NOTE Confidence: 0.9869861

00:36:12.700 --> 00:36:14.460 just, you know, identifying the

NOTE Confidence: 0.9869861

00:36:14.460 --> 00:36:15.900 same sort of genes that

NOTE Confidence: 0.9869861

00:36:15.900 --> 00:36:17.360 tolerate genetic variation?

NOTE Confidence: 0.9973192

00:36:17.820 --> 00:36:18.700 But I'd like to say

NOTE Confidence: 0.9973192

00:36:18.700 --> 00:36:19.500 that when you look at

NOTE Confidence: 0.9973192

00:36:19.500 --> 00:36:21.040 the pathways in a

NOTE Confidence: 0.9752762

00:36:21.340 --> 00:36:23.260 single cell type, maybe you'll

NOTE Confidence: 0.9752762

00:36:23.260 --> 00:36:23.760 find,

NOTE Confidence: 0.9691692

00:36:24.555 --> 00:36:26.875 actual biologically relevant information. And

NOTE Confidence: 0.9691692

00:36:26.875 --> 00:36:27.515 so that's what we tried

NOTE Confidence: 0.9691692

00:36:27.515 --> 00:36:28.974 to do with endothelial cells.

NOTE Confidence: 0.96434855

00:36:29.675 --> 00:36:31.515 So we created two different

NOTE Confidence: 0.96434855

00:36:31.515 --> 00:36:33.355 genetic risk scores for for

NOTE Confidence: 0.96434855

00:36:33.515 --> 00:36:34.555 from the GWAS data that

NOTE Confidence: 0.96434855

00:36:34.555 --> 00:36:36.155 we had. We created an

NOTE Confidence: 0.96434855

00:36:36.155 --> 00:36:37.915 endothelial cell genetic risk score

NOTE Confidence: 0.96434855

00:36:37.915 --> 00:36:39.770 with those, thirty five SNPs.

NOTE Confidence: 0.96434855

00:36:39.770 --> 00:36:40.810 There were forty one, but

NOTE Confidence: 0.96434855

00:36:40.810 --> 00:36:41.770 thirty five were sort of

NOTE Confidence: 0.96434855

00:36:41.770 --> 00:36:42.910 reproducibly genotyped.

NOTE Confidence: 0.97857004

00:36:43.609 --> 00:36:45.210 That's from our perturbseq data.

NOTE Confidence: 0.97857004

00:36:45.210 --> 00:36:46.590 Right? The the the big,

NOTE Confidence: 0.97857004

00:36:46.730 --> 00:36:48.170 you know, very expensive experiment

NOTE Confidence: 0.97857004

00:36:48.170 --> 00:36:49.050 that took my lab four

NOTE Confidence: 0.97857004

00:36:49.050 --> 00:36:50.650 years. And then we took

NOTE Confidence: 0.97857004

00:36:50.650 --> 00:36:52.250 forty seven forty six SNPs

NOTE Confidence: 0.97857004

00:36:52.250 --> 00:36:53.609 that are associated with LDL

NOTE Confidence: 0.97857004

00:36:53.609 --> 00:36:54.855 cholesterol. And we went to

NOTE Confidence: 0.97857004

00:36:54.855 --> 00:36:56.135 the UK Biobank, and you

NOTE Confidence: 0.97857004

00:36:56.135 --> 00:36:57.175 see that if you create

NOTE Confidence: 0.97857004

00:36:57.175 --> 00:36:59.114 different categories of patients,

NOTE Confidence: 0.94899017

00:36:59.815 --> 00:37:01.355 these two scores are additive.

NOTE Confidence: 0.9938035

00:37:01.815 --> 00:37:02.935 That the people with the

NOTE Confidence: 0.9938035

00:37:02.935 --> 00:37:04.614 highest number of coronary disease

NOTE Confidence: 0.9938035

00:37:04.614 --> 00:37:05.975 events after twelve years of

NOTE Confidence: 0.9938035

00:37:05.975 --> 00:37:06.475 follow-up,

NOTE Confidence: 0.9558428

00:37:07.020 --> 00:37:08.380 They have bad endothelial cells

NOTE Confidence: 0.9558428

00:37:08.380 --> 00:37:09.680 and they have bad lipid.

NOTE Confidence: 0.9558428

00:37:09.739 --> 00:37:10.480 And and,

NOTE Confidence: 0.9781587

00:37:11.180 --> 00:37:12.860 you know, as independent risk

NOTE Confidence: 0.9781587

00:37:12.860 --> 00:37:13.360 factors,

NOTE Confidence: 0.9423048

00:37:13.820 --> 00:37:15.020 this is sort of convincing

NOTE Confidence: 0.9423048

00:37:15.020 --> 00:37:16.480 in these statin naive patients.

NOTE Confidence: 0.99550897

00:37:16.940 --> 00:37:18.480 But with LDL cholesterol,

NOTE Confidence: 0.99908465

00:37:19.020 --> 00:37:20.540 right, you can just measure

NOTE Confidence: 0.99908465

00:37:20.540 --> 00:37:21.580 LDL. You don't need a

NOTE Confidence: 0.99908465

00:37:21.580 --> 00:37:23.255 genetic risk score for LDL

NOTE Confidence: 0.98694736

00:37:23.635 --> 00:37:24.835 cholesterol. You can just measure

NOTE Confidence: 0.98694736

00:37:24.835 --> 00:37:25.734 the serum levels.

NOTE Confidence: 0.9933959

00:37:26.035 --> 00:37:27.894 But for endothelial cell dysfunction,

NOTE Confidence: 0.9933959

00:37:28.035 --> 00:37:29.815 there is no measurable factor.

NOTE Confidence: 0.97712815

00:37:30.194 --> 00:37:31.954 Maybe hypertension, but well, I'll

NOTE Confidence: 0.97712815

00:37:31.954 --> 00:37:33.075 show you that, you know,

NOTE Confidence: 0.97712815

00:37:33.075 --> 00:37:34.674 perhaps not hypertension. Maybe this

NOTE Confidence: 0.97712815

00:37:34.674 --> 00:37:35.494 is an independent,

NOTE Confidence: 0.96827304

00:37:36.430 --> 00:37:38.610 pathway. But, certainly, this endothelial

NOTE Confidence: 0.96827304

00:37:38.670 --> 00:37:39.870 risk score does not correlate

NOTE Confidence: 0.96827304

00:37:39.870 --> 00:37:41.310 at all with LDL cholesterol

NOTE Confidence: 0.96827304

00:37:41.310 --> 00:37:42.290 as you see here.

NOTE Confidence: 0.9920801

00:37:43.070 --> 00:37:44.190 And then when we look

NOTE Confidence: 0.9920801

00:37:44.190 --> 00:37:45.250 at UK Biobank,

NOTE Confidence: 0.98539525

00:37:45.630 --> 00:37:46.590 sort of, you know, the

NOTE Confidence: 0.98539525

00:37:46.590 --> 00:37:48.290 the the sort of classic

NOTE Confidence: 0.98539525

00:37:48.350 --> 00:37:49.170 table one,

NOTE Confidence: 0.9963353

00:37:49.475 --> 00:37:51.075 Our endothelial cell risk score

NOTE Confidence: 0.9963353

00:37:51.075 --> 00:37:52.775 doesn't really correlate with much.

NOTE Confidence: 0.9977372

00:37:53.075 --> 00:37:54.114 There is sort of a

NOTE Confidence: 0.9977372

00:37:54.114 --> 00:37:55.895 nominal correlation with hypertension,

NOTE Confidence: 0.98806506

00:37:57.075 --> 00:37:59.075 and a nominal correlation with,

NOTE Confidence: 0.86110914

00:37:59.715 --> 00:38:00.614 kidney function.

NOTE Confidence: 0.9769059

00:38:00.995 --> 00:38:01.955 But when you actually look

NOTE Confidence: 0.9769059

00:38:01.955 --> 00:38:02.995 at the numbers, it's pretty

NOTE Confidence: 0.9769059

00:38:02.995 --> 00:38:04.195 minimal. So the people with

NOTE Confidence: 0.9769059

00:38:04.195 --> 00:38:06.140 the best endothelial score, the

NOTE Confidence: 0.9769059

00:38:06.140 --> 00:38:07.980 lowest twenty percent, five point

NOTE Confidence: 0.9769059

00:38:07.980 --> 00:38:09.360 four percent of them have

NOTE Confidence: 0.9769059

00:38:09.580 --> 00:38:10.400 of hypertension,

NOTE Confidence: 0.99919075

00:38:10.780 --> 00:38:11.660 and the people with the

NOTE Confidence: 0.99919075

00:38:11.660 --> 00:38:12.160 worst,

NOTE Confidence: 0.95831984

00:38:12.460 --> 00:38:14.060 endothelial risk score, six point

NOTE Confidence: 0.95831984

00:38:14.060 --> 00:38:16.000 two percent have hypertension. Right?

NOTE Confidence: 0.95831984

00:38:16.220 --> 00:38:17.020 You know, I wouldn't say

NOTE Confidence: 0.95831984

00:38:17.020 --> 00:38:18.460 that that's really driving the

NOTE Confidence: 0.95831984

00:38:18.460 --> 00:38:20.320 biological effect of this score.

NOTE Confidence: 0.9198367

00:38:20.675 --> 00:38:22.515 And same thing with, the

NOTE Confidence: 0.9198367

00:38:22.515 --> 00:38:23.494 the eGFR.

NOTE Confidence: 0.9646961

00:38:23.795 --> 00:38:25.395 Right? It's it's though it's

NOTE Confidence: 0.9646961

00:38:25.395 --> 00:38:26.915 nominally significant, it's really a

NOTE Confidence: 0.9646961

00:38:26.915 --> 00:38:28.275 minimal direction of effect. And

NOTE Confidence: 0.9646961

00:38:28.275 --> 00:38:29.075 and this this is sort

NOTE Confidence: 0.9646961

00:38:29.075 --> 00:38:29.955 of the list of snips

NOTE Confidence: 0.9646961

00:38:29.955 --> 00:38:30.915 that we included in the

NOTE Confidence: 0.9646961

00:38:30.915 --> 00:38:31.415 score.

NOTE Confidence: 0.95412195

00:38:31.715 --> 00:38:33.090 But then when you again,

NOTE Confidence: 0.95412195

00:38:33.090 --> 00:38:34.610 in UK Biobank sort of

NOTE Confidence: 0.95412195

00:38:34.610 --> 00:38:36.470 create different levels of score,

NOTE Confidence: 0.96932185

00:38:36.850 --> 00:38:37.970 there is an EC risk

NOTE Confidence: 0.96932185

00:38:37.970 --> 00:38:39.010 score and a lipid risk

NOTE Confidence: 0.96932185

00:38:39.010 --> 00:38:40.210 score. The people far and

NOTE Confidence: 0.96932185

00:38:40.210 --> 00:38:41.810 away with the most events

NOTE Confidence: 0.96932185

00:38:41.810 --> 00:38:43.010 have a bad EC risk

NOTE Confidence: 0.96932185

00:38:43.010 --> 00:38:44.130 score and a bad lipid

NOTE Confidence: 0.96932185

00:38:44.130 --> 00:38:44.870 risk score.

NOTE Confidence: 0.9749157

00:38:45.410 --> 00:38:47.570 And then the second highest

NOTE Confidence: 0.9749157

00:38:47.570 --> 00:38:49.215 risk group is is bad

NOTE Confidence: 0.9749157

00:38:49.215 --> 00:38:50.655 EC risk score, but low

NOTE Confidence: 0.9749157

00:38:50.655 --> 00:38:51.855 lipid risk score. Right? So

NOTE Confidence: 0.9749157

00:38:51.855 --> 00:38:52.815 the EC risk score is,

NOTE Confidence: 0.9749157

00:38:52.815 --> 00:38:53.875 like, the most predictive

NOTE Confidence: 0.98482347

00:38:54.575 --> 00:38:56.015 of poor outcomes. And some

NOTE Confidence: 0.98482347

00:38:56.015 --> 00:38:57.375 of that might be because

NOTE Confidence: 0.98482347

00:38:57.375 --> 00:38:58.815 statins exist in this world.

NOTE Confidence: 0.98482347

00:38:58.815 --> 00:38:59.775 Right? When you have a

NOTE Confidence: 0.98482347

00:38:59.775 --> 00:39:00.989 bad lipid risk score, it's

NOTE Confidence: 0.98482347

00:39:00.989 --> 00:39:02.350 treatable, whereas the endothelial risk

NOTE Confidence: 0.98482347

00:39:02.350 --> 00:39:03.230 score is not. Right? So

NOTE Confidence: 0.98482347

00:39:03.230 --> 00:39:04.030 these are this is a

NOTE Confidence: 0.98482347

00:39:04.030 --> 00:39:05.170 unique group of patients.

NOTE Confidence: 0.9687776

00:39:05.630 --> 00:39:06.510 But we wanted to see

NOTE Confidence: 0.9687776

00:39:06.510 --> 00:39:07.150 if there was, like, a

NOTE Confidence: 0.9687776

00:39:07.150 --> 00:39:08.670 treatment interaction that was unique.

NOTE Confidence: 0.9687776

00:39:08.670 --> 00:39:09.469 So we went to the

NOTE Confidence: 0.9687776

00:39:09.469 --> 00:39:11.150 JUPITER trial. Right? And and

NOTE Confidence: 0.9687776

00:39:11.150 --> 00:39:12.350 all this genomic data is

NOTE Confidence: 0.9687776

00:39:12.350 --> 00:39:13.415 sort of housed, you know,

NOTE Confidence: 0.9687776

00:39:13.415 --> 00:39:14.695 paid for by drug companies,

NOTE Confidence: 0.9687776

00:39:14.695 --> 00:39:16.055 housed at the Brigham, and

NOTE Confidence: 0.9687776

00:39:16.055 --> 00:39:17.255 not touched at all. Right?

NOTE Confidence: 0.9687776

00:39:17.255 --> 00:39:19.015 No one studies these, genetic

NOTE Confidence: 0.9687776

00:39:19.015 --> 00:39:20.135 risk scores and true clinical

NOTE Confidence: 0.9687776

00:39:20.135 --> 00:39:21.015 trial data. So we thought

NOTE Confidence: 0.9687776

00:39:21.015 --> 00:39:22.234 it was a unique opportunity.

NOTE Confidence: 0.9792197

00:39:22.695 --> 00:39:23.415 And so we took our

NOTE Confidence: 0.9792197

00:39:23.415 --> 00:39:24.535 endothelial risk score, and we

NOTE Confidence: 0.9792197

00:39:24.535 --> 00:39:25.655 went to the JUPITER trial,

NOTE Confidence: 0.9792197

00:39:25.655 --> 00:39:26.810 which was rosuvastatin

NOTE Confidence: 0.97337395

00:39:27.350 --> 00:39:28.790 randomized to people who had

NOTE Confidence: 0.97337395

00:39:28.790 --> 00:39:30.230 never had a coronary artery

NOTE Confidence: 0.97337395

00:39:30.230 --> 00:39:31.750 event. So primary prevention of

NOTE Confidence: 0.97337395

00:39:31.750 --> 00:39:33.370 coronary artery disease.

NOTE Confidence: 0.9760307

00:39:33.670 --> 00:39:34.710 And what you see is

NOTE Confidence: 0.9760307

00:39:34.710 --> 00:39:37.050 this remarkable treatment effect. So

NOTE Confidence: 0.9805073

00:39:37.590 --> 00:39:38.870 the hazard ratio is point

NOTE Confidence: 0.9805073

00:39:38.870 --> 00:39:40.150 two eight. There's,

NOTE Confidence: 0.95410705

00:39:40.630 --> 00:39:41.910 a absolute risk reduction of

NOTE Confidence: 0.95410705

00:39:41.910 --> 00:39:43.105 two two point two

NOTE Confidence: 0.96836156

00:39:43.484 --> 00:39:45.424 percent, and there's this, gradient

NOTE Confidence: 0.96836156

00:39:45.645 --> 00:39:46.765 that the people with low

NOTE Confidence: 0.96836156

00:39:46.765 --> 00:39:47.984 endothelial risk scores,

NOTE Confidence: 0.99984837

00:39:48.364 --> 00:39:48.864 don't

NOTE Confidence: 0.99301857

00:39:49.484 --> 00:39:51.085 have much benefit from being

NOTE Confidence: 0.99301857

00:39:51.085 --> 00:39:52.464 treated with with rosuvastatin,

NOTE Confidence: 0.99017996

00:39:52.765 --> 00:39:53.964 but the people with really

NOTE Confidence: 0.99017996

00:39:53.964 --> 00:39:55.080 bad endothelial cells

NOTE Confidence: 0.9892328

00:39:55.719 --> 00:39:57.480 drive the strongest benefit from

NOTE Confidence: 0.9892328

00:39:57.480 --> 00:39:58.540 being treated with rosuvastatin.

NOTE Confidence: 0.96537006

00:39:59.320 --> 00:40:00.360 And when you compare that

NOTE Confidence: 0.96537006

00:40:00.360 --> 00:40:01.400 to, like, the other risk

NOTE Confidence: 0.96537006

00:40:01.400 --> 00:40:02.280 scores you can make, so

NOTE Confidence: 0.96537006

00:40:02.280 --> 00:40:03.080 you could take all the

NOTE Confidence: 0.96537006

00:40:03.080 --> 00:40:04.200 other variants that aren't in

NOTE Confidence: 0.96537006

00:40:04.200 --> 00:40:05.260 the EC pathway.

NOTE Confidence: 0.9875478

00:40:06.120 --> 00:40:08.040 There's obviously benefit, but there's

NOTE Confidence: 0.9875478

00:40:08.040 --> 00:40:09.400 benefit at every level of

NOTE Confidence: 0.9875478

00:40:09.400 --> 00:40:10.460 that risk score.

NOTE Confidence: 0.9782589

00:40:11.025 --> 00:40:13.184 And the top group doesn't

NOTE Confidence: 0.9782589

00:40:13.184 --> 00:40:14.785 drive the same degree of

NOTE Confidence: 0.9782589

00:40:14.785 --> 00:40:16.325 benefit in this study.

NOTE Confidence: 0.9843674

00:40:16.785 --> 00:40:17.984 And then if you take

NOTE Confidence: 0.9843674

00:40:17.984 --> 00:40:19.105 the lipid risk score and

NOTE Confidence: 0.9843674

00:40:19.105 --> 00:40:20.145 now this is the opposite

NOTE Confidence: 0.9843674

00:40:20.145 --> 00:40:21.025 of what we expected to

NOTE Confidence: 0.9843674

00:40:21.025 --> 00:40:21.984 see. We thought a lipid

NOTE Confidence: 0.9843674

00:40:21.984 --> 00:40:24.120 lowering drug would work best

NOTE Confidence: 0.9843674

00:40:24.200 --> 00:40:25.900 on people with high genetically

NOTE Confidence: 0.9843674

00:40:25.960 --> 00:40:26.780 driven lipids.

NOTE Confidence: 0.970567

00:40:27.560 --> 00:40:28.460 And, again,

NOTE Confidence: 0.9873685

00:40:28.840 --> 00:40:30.200 every level of the lipid

NOTE Confidence: 0.9873685

00:40:30.200 --> 00:40:31.320 risk score, they derive the

NOTE Confidence: 0.9873685

00:40:31.320 --> 00:40:32.520 sort of same benefit to

NOTE Confidence: 0.9873685

00:40:32.520 --> 00:40:33.020 rosuvastatin.

NOTE Confidence: 0.99960417

00:40:33.880 --> 00:40:35.080 And even in the top

NOTE Confidence: 0.99960417

00:40:35.080 --> 00:40:35.580 category,

NOTE Confidence: 0.9960084

00:40:35.960 --> 00:40:37.480 this score actually performed the

NOTE Confidence: 0.9960084

00:40:37.480 --> 00:40:37.875 worst

NOTE Confidence: 0.99259955

00:40:38.355 --> 00:40:38.755 that,

NOTE Confidence: 0.9898305

00:40:39.315 --> 00:40:40.275 people with high,

NOTE Confidence: 0.98855823

00:40:40.835 --> 00:40:42.755 genetically driven high LDL have

NOTE Confidence: 0.98855823

00:40:42.755 --> 00:40:44.614 the the worst response

NOTE Confidence: 0.9736939

00:40:45.395 --> 00:40:45.875 to,

NOTE Confidence: 0.9922352

00:40:46.435 --> 00:40:48.035 to rosuvastatin compared to other

NOTE Confidence: 0.9922352

00:40:48.035 --> 00:40:49.555 genomic risk scores that were

NOTE Confidence: 0.9922352

00:40:49.555 --> 00:40:50.695 independent pathways.

NOTE Confidence: 0.9216086

00:40:51.155 --> 00:40:52.835 So sort of unexpected result.

NOTE Confidence: 0.9216086

00:40:52.835 --> 00:40:53.635 We weren't sure if it

NOTE Confidence: 0.9216086

00:40:53.635 --> 00:40:55.050 was true. So we went

NOTE Confidence: 0.9216086

00:40:55.050 --> 00:40:56.250 to the Fourier trial, right,

NOTE Confidence: 0.9216086

00:40:56.250 --> 00:40:57.690 the PCSK9 trial that our

NOTE Confidence: 0.9216086

00:40:57.690 --> 00:40:58.410 own knee hard to say

NOTE Confidence: 0.9216086

00:40:58.410 --> 00:40:59.130 or your own knee hard

NOTE Confidence: 0.9216086

00:40:59.130 --> 00:40:59.850 to say, I should say,

NOTE Confidence: 0.9216086

00:40:59.850 --> 00:41:00.350 unfortunately.

NOTE Confidence: 0.95662373

00:41:00.970 --> 00:41:01.770 Your own knee hard to

NOTE Confidence: 0.95662373

00:41:01.770 --> 00:41:02.410 say was one of the

NOTE Confidence: 0.95662373

00:41:02.410 --> 00:41:03.290 leaders of. And,

NOTE Confidence: 0.89339846

00:41:03.850 --> 00:41:05.630 obviously, you know, an orthogonal

NOTE Confidence: 0.9995635

00:41:06.485 --> 00:41:08.105 treatment for LDL cholesterol

NOTE Confidence: 0.73093605

00:41:08.645 --> 00:41:09.145 and,

NOTE Confidence: 0.9322496

00:41:09.445 --> 00:41:11.364 now secondary prevention trial, much

NOTE Confidence: 0.9322496

00:41:11.364 --> 00:41:12.265 sicker patients,

NOTE Confidence: 0.97156054

00:41:13.205 --> 00:41:14.645 who have have a higher

NOTE Confidence: 0.97156054

00:41:14.645 --> 00:41:16.245 event rate. And all these

NOTE Confidence: 0.97156054

00:41:16.245 --> 00:41:17.205 patients are also on a

NOTE Confidence: 0.97156054

00:41:17.205 --> 00:41:18.565 statin therapy. So that also

NOTE Confidence: 0.97156054

00:41:18.565 --> 00:41:20.085 kinda confounds the effect of

NOTE Confidence: 0.97156054

00:41:20.085 --> 00:41:21.045 lipids a bit, but, you

NOTE Confidence: 0.97156054

00:41:21.045 --> 00:41:21.765 know, we thought it was

NOTE Confidence: 0.97156054

00:41:21.765 --> 00:41:22.890 a a unique population to

NOTE Confidence: 0.97156054

00:41:22.890 --> 00:41:24.569 study. And, again, genetics are

NOTE Confidence: 0.97156054

00:41:24.569 --> 00:41:26.089 available in this population. And

NOTE Confidence: 0.97156054

00:41:26.089 --> 00:41:26.589 so,

NOTE Confidence: 0.954871

00:41:27.530 --> 00:41:29.069 again, you see the the

NOTE Confidence: 0.954871

00:41:29.290 --> 00:41:30.809 the effect sizes are smaller.

NOTE Confidence: 0.954871

00:41:30.809 --> 00:41:32.190 They're, like, a bit attenuated,

NOTE Confidence: 0.95955825

00:41:32.890 --> 00:41:34.589 in each risk score. But

NOTE Confidence: 0.95955825

00:41:34.695 --> 00:41:35.575 on the left, you see

NOTE Confidence: 0.95955825

00:41:35.575 --> 00:41:37.495 the EC risk score and

NOTE Confidence: 0.95955825

00:41:37.495 --> 00:41:38.855 really no benefit in the

NOTE Confidence: 0.95955825

00:41:38.855 --> 00:41:40.315 low and middle risk categories,

NOTE Confidence: 0.95955825

00:41:40.375 --> 00:41:41.755 you know, very modest benefit

NOTE Confidence: 0.95955825

00:41:41.815 --> 00:41:42.955 with, nonsignificant

NOTE Confidence: 0.97185314

00:41:43.335 --> 00:41:44.155 hazard ratios.

NOTE Confidence: 0.95431507

00:41:44.535 --> 00:41:45.735 But in the highest risk

NOTE Confidence: 0.95431507

00:41:45.735 --> 00:41:47.335 category, there was the strongest

NOTE Confidence: 0.95431507

00:41:47.335 --> 00:41:48.695 absolute risk reduction of four

NOTE Confidence: 0.95431507

00:41:48.695 --> 00:41:50.660 point four percent. It was

NOTE Confidence: 0.95431507

00:41:50.660 --> 00:41:51.160 significant.

NOTE Confidence: 0.9580201

00:41:51.539 --> 00:41:53.460 Whereas in the non EC

NOTE Confidence: 0.9580201

00:41:53.460 --> 00:41:54.200 risk score,

NOTE Confidence: 0.9597383

00:41:54.500 --> 00:41:56.359 again, very minimal improvement,

NOTE Confidence: 0.9830053

00:41:56.660 --> 00:41:58.200 no gradient of benefit.

NOTE Confidence: 0.977943

00:41:58.900 --> 00:42:00.980 And even more disappointingly, in

NOTE Confidence: 0.977943

00:42:00.980 --> 00:42:02.285 the lipid risk score, it

NOTE Confidence: 0.977943

00:42:02.285 --> 00:42:03.405 was it was a null

NOTE Confidence: 0.977943

00:42:03.405 --> 00:42:04.765 association. There was no gradient

NOTE Confidence: 0.977943

00:42:04.765 --> 00:42:05.425 of benefit.

NOTE Confidence: 0.9593024

00:42:06.125 --> 00:42:07.325 So we found this intriguing.

NOTE Confidence: 0.9593024

00:42:07.325 --> 00:42:08.205 Right? It was the opposite

NOTE Confidence: 0.9593024

00:42:08.205 --> 00:42:09.245 of what we wanted this

NOTE Confidence: 0.9593024

00:42:09.245 --> 00:42:10.125 show. I we thought it

NOTE Confidence: 0.9593024

00:42:10.125 --> 00:42:11.485 was a very simple paper

NOTE Confidence: 0.9593024

00:42:11.485 --> 00:42:12.364 to write that, you know,

NOTE Confidence: 0.9593024

00:42:12.364 --> 00:42:13.739 the EC risk score is

NOTE Confidence: 0.9593024

00:42:13.980 --> 00:42:16.000 completely independent of LDL biology.

NOTE Confidence: 0.99171394

00:42:17.500 --> 00:42:19.260 And, the the EC risk

NOTE Confidence: 0.99171394

00:42:19.260 --> 00:42:20.300 score should have its own

NOTE Confidence: 0.99171394

00:42:20.300 --> 00:42:20.800 therapies.

NOTE Confidence: 0.9508721

00:42:21.180 --> 00:42:22.140 And what we're sort of

NOTE Confidence: 0.9508721

00:42:22.140 --> 00:42:23.100 saying now, which I'll sort

NOTE Confidence: 0.9508721

00:42:23.100 --> 00:42:23.900 of dig into a little

NOTE Confidence: 0.9508721

00:42:23.900 --> 00:42:25.020 more, is that, well, the

NOTE Confidence: 0.9508721

00:42:25.020 --> 00:42:26.060 EC risk score is an

NOTE Confidence: 0.9508721

00:42:26.060 --> 00:42:26.900 independent re

NOTE Confidence: 0.9832134

00:42:27.420 --> 00:42:29.035 predictor of risk, but but

NOTE Confidence: 0.9832134

00:42:29.035 --> 00:42:30.075 it predicts the people who

NOTE Confidence: 0.9832134

00:42:30.075 --> 00:42:31.435 benefit the most from LDL

NOTE Confidence: 0.9832134

00:42:31.435 --> 00:42:33.114 lowering therapy. Right? And so,

NOTE Confidence: 0.9832134

00:42:33.114 --> 00:42:34.075 you know, that we have

NOTE Confidence: 0.9832134

00:42:34.075 --> 00:42:35.114 to sort of dig into

NOTE Confidence: 0.9832134

00:42:35.114 --> 00:42:36.315 the mechanism behind that a

NOTE Confidence: 0.9832134

00:42:36.315 --> 00:42:37.355 bit. And so we went

NOTE Confidence: 0.9832134

00:42:37.355 --> 00:42:38.875 back to UK Biobank, and

NOTE Confidence: 0.9832134

00:42:38.875 --> 00:42:39.995 what you see is each

NOTE Confidence: 0.9832134

00:42:39.995 --> 00:42:41.275 one of these are,

NOTE Confidence: 0.981824

00:42:41.835 --> 00:42:43.310 you know, tens of thousands

NOTE Confidence: 0.981824

00:42:43.310 --> 00:42:44.910 of patients who had different

NOTE Confidence: 0.981824

00:42:44.910 --> 00:42:46.830 baseline LDL values in the

NOTE Confidence: 0.981824

00:42:46.830 --> 00:42:47.650 UK Biobank.

NOTE Confidence: 0.9924282

00:42:48.030 --> 00:42:48.770 And so,

NOTE Confidence: 0.92868793

00:42:49.390 --> 00:42:50.770 people who had a LDL

NOTE Confidence: 0.9981174

00:42:51.150 --> 00:42:52.530 greater than one ninety

NOTE Confidence: 0.9830789

00:42:52.910 --> 00:42:54.510 for on the x axis

NOTE Confidence: 0.9830789

00:42:54.510 --> 00:42:56.130 is every level of polygenic

NOTE Confidence: 0.9830789

00:42:56.350 --> 00:42:57.570 risk score in the population.

NOTE Confidence: 0.9904082

00:42:58.175 --> 00:42:58.614 So,

NOTE Confidence: 0.9838451

00:42:59.055 --> 00:42:59.875 when when

NOTE Confidence: 0.971681

00:43:00.335 --> 00:43:01.215 and this is just the

NOTE Confidence: 0.971681

00:43:01.215 --> 00:43:02.895 endothelial cell polygenic risk score.

NOTE Confidence: 0.971681

00:43:02.895 --> 00:43:03.935 And so people with very

NOTE Confidence: 0.971681

00:43:03.935 --> 00:43:05.775 high LDL, there's this huge

NOTE Confidence: 0.971681

00:43:05.775 --> 00:43:07.455 gradient of benefit. Right? They

NOTE Confidence: 0.971681

00:43:07.455 --> 00:43:10.015 have the highest risk derived

NOTE Confidence: 0.971681

00:43:10.015 --> 00:43:11.875 from bad endothelial cell function.

NOTE Confidence: 0.97989196

00:43:12.420 --> 00:43:12.920 And,

NOTE Confidence: 0.97397625

00:43:13.619 --> 00:43:15.219 but when people have normal

NOTE Confidence: 0.97397625

00:43:15.219 --> 00:43:17.079 or or even low LDL,

NOTE Confidence: 0.97397625

00:43:17.219 --> 00:43:18.359 like the blue line,

NOTE Confidence: 0.97692263

00:43:18.660 --> 00:43:20.440 there's actually almost no benefit.

NOTE Confidence: 0.97692263

00:43:20.660 --> 00:43:21.940 I mean, there's no gradient

NOTE Confidence: 0.97692263

00:43:21.940 --> 00:43:23.219 of risk from the endothelial

NOTE Confidence: 0.97692263

00:43:23.219 --> 00:43:24.099 risk score. So, again, I'm

NOTE Confidence: 0.97692263

00:43:24.099 --> 00:43:25.224 I'm sort of saying this

NOTE Confidence: 0.97692263

00:43:25.224 --> 00:43:26.905 point over again that the

NOTE Confidence: 0.97692263

00:43:26.905 --> 00:43:27.805 the interaction

NOTE Confidence: 0.97666264

00:43:28.105 --> 00:43:30.425 between endothelial cell function and

NOTE Confidence: 0.97666264

00:43:30.425 --> 00:43:32.185 either genetically low LDL or

NOTE Confidence: 0.97666264

00:43:32.185 --> 00:43:34.025 pharmacologically low LDL seems to

NOTE Confidence: 0.97666264

00:43:34.025 --> 00:43:35.145 be showing up in UK

NOTE Confidence: 0.97666264

00:43:35.145 --> 00:43:37.145 Biobank, the JUPITER trial, and

NOTE Confidence: 0.97666264

00:43:37.145 --> 00:43:38.100 the Fourier trial.

NOTE Confidence: 0.99043417

00:43:38.660 --> 00:43:39.780 And, again, this is just

NOTE Confidence: 0.99043417

00:43:39.780 --> 00:43:41.140 another way of showing this

NOTE Confidence: 0.99043417

00:43:41.140 --> 00:43:43.140 sort of interaction. So in

NOTE Confidence: 0.99043417

00:43:43.140 --> 00:43:43.960 UK Biobank,

NOTE Confidence: 0.9878492

00:43:44.500 --> 00:43:45.460 on the x axis is

NOTE Confidence: 0.9878492

00:43:45.460 --> 00:43:47.300 the baseline LDL. And what

NOTE Confidence: 0.9878492

00:43:47.300 --> 00:43:48.020 you see on the left

NOTE Confidence: 0.9878492

00:43:48.020 --> 00:43:49.140 side is people in UK

NOTE Confidence: 0.9878492

00:43:49.140 --> 00:43:50.420 Biobank who have a baseline

NOTE Confidence: 0.9878492

00:43:50.420 --> 00:43:51.560 LDL of fifty.

NOTE Confidence: 0.98819906

00:43:52.105 --> 00:43:53.864 There's no hazard from having

NOTE Confidence: 0.98819906

00:43:53.864 --> 00:43:55.145 a bad endothelial cell risk

NOTE Confidence: 0.98819906

00:43:55.145 --> 00:43:55.645 score.

NOTE Confidence: 0.98749775

00:43:55.945 --> 00:43:56.905 But on the right side

NOTE Confidence: 0.98749775

00:43:56.905 --> 00:43:58.445 are people with baseline LDLs

NOTE Confidence: 0.98749775

00:43:58.505 --> 00:44:00.025 of one ninety, and they

NOTE Confidence: 0.98749775

00:44:00.025 --> 00:44:01.565 have the strongest hazard.

NOTE Confidence: 0.99922395

00:44:02.265 --> 00:44:03.705 If you compare that to

NOTE Confidence: 0.99922395

00:44:03.705 --> 00:44:05.165 an LDL risk score,

NOTE Confidence: 0.9949586

00:44:05.589 --> 00:44:06.869 their risk is the same

NOTE Confidence: 0.9949586

00:44:06.869 --> 00:44:08.069 no matter what their baseline

NOTE Confidence: 0.9949586

00:44:08.069 --> 00:44:09.670 LDL is. Right? So,

NOTE Confidence: 0.9075838

00:44:10.309 --> 00:44:11.050 the the

NOTE Confidence: 0.8959619

00:44:12.710 --> 00:44:13.989 the the increased risk from

NOTE Confidence: 0.8959619

00:44:13.989 --> 00:44:15.130 having bad LDL

NOTE Confidence: 0.9631373

00:44:15.510 --> 00:44:17.130 is present at every level

NOTE Confidence: 0.9631373

00:44:17.190 --> 00:44:18.630 of of baseline LDL, a

NOTE Confidence: 0.9631373

00:44:18.630 --> 00:44:19.785 very, very sort of different,

NOTE Confidence: 0.9631373

00:44:20.184 --> 00:44:22.025 biologic effect. And so why

NOTE Confidence: 0.9631373

00:44:22.025 --> 00:44:22.984 could this be? Right? What

NOTE Confidence: 0.9631373

00:44:22.984 --> 00:44:24.025 what is the mechanism behind

NOTE Confidence: 0.9631373

00:44:24.025 --> 00:44:25.065 this? Is this real? Does

NOTE Confidence: 0.9631373

00:44:25.065 --> 00:44:26.184 this make any sense? And

NOTE Confidence: 0.9631373

00:44:26.184 --> 00:44:26.984 this is where we started

NOTE Confidence: 0.9631373

00:44:26.984 --> 00:44:28.424 looking at Bill Sessa's paper

NOTE Confidence: 0.9631373

00:44:28.424 --> 00:44:29.164 from Yale

NOTE Confidence: 0.9795364

00:44:29.464 --> 00:44:30.184 that, you know, he has

NOTE Confidence: 0.9795364

00:44:30.184 --> 00:44:31.065 this line in a lot

NOTE Confidence: 0.9795364

00:44:31.065 --> 00:44:32.025 of his papers that the

NOTE Confidence: 0.9795364

00:44:32.025 --> 00:44:33.864 transport of LDL cholesterol into

NOTE Confidence: 0.9795364

00:44:33.864 --> 00:44:34.525 the subendothelial

NOTE Confidence: 0.99886346

00:44:34.905 --> 00:44:36.469 space is the fuel for

NOTE Confidence: 0.99886346

00:44:36.469 --> 00:44:38.010 the fire that drives atherosclerosis.

NOTE Confidence: 0.99886346

00:44:38.309 --> 00:44:38.809 Right?

NOTE Confidence: 0.98942095

00:44:39.430 --> 00:44:40.869 LDL is high throughout your

NOTE Confidence: 0.98942095

00:44:40.869 --> 00:44:41.369 body,

NOTE Confidence: 0.9866028

00:44:41.750 --> 00:44:43.369 but only in,

NOTE Confidence: 0.99208546

00:44:43.670 --> 00:44:45.369 certain spots do you develop

NOTE Confidence: 0.98234624

00:44:45.910 --> 00:44:46.950 plaques. And, you know, we

NOTE Confidence: 0.98234624

00:44:47.030 --> 00:44:48.309 we've all had theories on

NOTE Confidence: 0.98234624

00:44:48.309 --> 00:44:49.594 that. It's turbulent flow in

NOTE Confidence: 0.98234624

00:44:49.594 --> 00:44:51.614 some places. It's vascular injury.

NOTE Confidence: 0.93159086

00:44:52.635 --> 00:44:53.994 But it seems to be

NOTE Confidence: 0.93159086

00:44:53.994 --> 00:44:55.594 that there's a strong strong

NOTE Confidence: 0.93159086

00:44:55.594 --> 00:44:56.094 correlate,

NOTE Confidence: 0.9594496

00:44:56.395 --> 00:44:58.335 strong interaction between LDL

NOTE Confidence: 0.98318255

00:44:58.795 --> 00:45:00.575 and endothelial cell function.

NOTE Confidence: 0.99485344

00:45:01.130 --> 00:45:02.969 And the people where LDL

NOTE Confidence: 0.99485344

00:45:02.969 --> 00:45:04.570 is the most toxic are

NOTE Confidence: 0.99485344

00:45:04.570 --> 00:45:05.870 the people with bad endothelial

NOTE Confidence: 0.99485344

00:45:05.930 --> 00:45:07.370 cells driven by their poor

NOTE Confidence: 0.99485344

00:45:07.370 --> 00:45:09.050 genetics. And so that's sort

NOTE Confidence: 0.99485344

00:45:09.050 --> 00:45:10.010 of the summary of our

NOTE Confidence: 0.99485344

00:45:10.010 --> 00:45:10.510 paper.

NOTE Confidence: 0.97723764

00:45:10.810 --> 00:45:12.090 Now we're trying to study

NOTE Confidence: 0.97723764

00:45:12.090 --> 00:45:13.290 this sort of process of

NOTE Confidence: 0.97723764

00:45:13.290 --> 00:45:15.765 LDL uptake using phenotypic screens.

NOTE Confidence: 0.97723764

00:45:15.765 --> 00:45:16.645 And I I've sort of

NOTE Confidence: 0.97723764

00:45:16.645 --> 00:45:17.445 talked about this with some

NOTE Confidence: 0.97723764

00:45:17.445 --> 00:45:18.484 of the scientists who I've

NOTE Confidence: 0.97723764

00:45:18.484 --> 00:45:19.844 met with today. And and

NOTE Confidence: 0.97723764

00:45:19.844 --> 00:45:20.724 and, you know, I'm happy

NOTE Confidence: 0.97723764

00:45:20.724 --> 00:45:21.525 to share this data, but

NOTE Confidence: 0.97723764

00:45:21.525 --> 00:45:23.204 we've run these, like, genome

NOTE Confidence: 0.97723764

00:45:23.204 --> 00:45:24.565 wide CRISPR screens. And that's

NOTE Confidence: 0.97723764

00:45:24.565 --> 00:45:25.285 what I when I say

NOTE Confidence: 0.97723764

00:45:25.285 --> 00:45:27.045 that, like, functional biology can

NOTE Confidence: 0.97723764

00:45:27.045 --> 00:45:28.325 now be done at scale

NOTE Confidence: 0.97723764

00:45:28.325 --> 00:45:29.910 just like genetics was ten

NOTE Confidence: 0.97723764

00:45:29.910 --> 00:45:31.109 years ago. This is what

NOTE Confidence: 0.97723764

00:45:31.109 --> 00:45:31.910 I mean. Right? You can

NOTE Confidence: 0.97723764

00:45:31.910 --> 00:45:33.030 study the effect of every

NOTE Confidence: 0.97723764

00:45:33.030 --> 00:45:33.930 single gene,

NOTE Confidence: 0.9771436

00:45:34.710 --> 00:45:35.989 on LDL uptake. On the

NOTE Confidence: 0.9771436

00:45:35.989 --> 00:45:37.829 left is endothelial cells. Every

NOTE Confidence: 0.9771436

00:45:37.829 --> 00:45:38.869 gene involved in,

NOTE Confidence: 0.9198136

00:45:39.910 --> 00:45:41.349 LDL uptake and endothelial cells.

NOTE Confidence: 0.9198136

00:45:41.349 --> 00:45:42.550 And these are LDL receptor

NOTE Confidence: 0.9198136

00:45:42.550 --> 00:45:44.305 knockout endothelial cells. So we're

NOTE Confidence: 0.9198136

00:45:44.305 --> 00:45:45.745 working with Bill Sessa and

NOTE Confidence: 0.9198136

00:45:45.745 --> 00:45:47.045 hopefully Carlos Fernandez,

NOTE Confidence: 0.996743

00:45:47.585 --> 00:45:49.285 to look at what mechanisms

NOTE Confidence: 0.996743

00:45:49.505 --> 00:45:51.045 of disease are driving this.

NOTE Confidence: 0.9468536

00:45:51.425 --> 00:45:52.145 And then on the right,

NOTE Confidence: 0.9468536

00:45:52.145 --> 00:45:53.665 because Wolfram's here, basically, I

NOTE Confidence: 0.9468536

00:45:53.665 --> 00:45:54.945 I included our our work

NOTE Confidence: 0.9468536

00:45:54.945 --> 00:45:57.025 of of knocking out every

NOTE Confidence: 0.9468536

00:45:57.025 --> 00:45:58.420 gene in the genome in

NOTE Confidence: 0.9468536

00:45:58.420 --> 00:46:00.180 hepatocytes. And you, again, you

NOTE Confidence: 0.9468536

00:46:00.180 --> 00:46:02.500 rediscover, like, the entire cholesterol

NOTE Confidence: 0.9468536

00:46:02.500 --> 00:46:04.739 biosynthesis pathway. You rediscover the

NOTE Confidence: 0.9468536

00:46:04.739 --> 00:46:06.440 triglyceride synthesis pathway,

NOTE Confidence: 0.9529929

00:46:06.739 --> 00:46:07.780 but then you find new

NOTE Confidence: 0.9529929

00:46:07.780 --> 00:46:08.980 hits and new regulators of

NOTE Confidence: 0.9529929

00:46:08.980 --> 00:46:10.180 these pathways with these sort

NOTE Confidence: 0.9529929

00:46:10.180 --> 00:46:11.640 of pool genomic approaches.

NOTE Confidence: 0.9617894

00:46:12.425 --> 00:46:13.224 So I find this very

NOTE Confidence: 0.9617894

00:46:13.224 --> 00:46:14.744 exciting. And, again, I'm sort

NOTE Confidence: 0.9617894

00:46:14.744 --> 00:46:16.025 of saying, I've I'm I'm

NOTE Confidence: 0.9617894

00:46:16.025 --> 00:46:17.625 taking my mechanistic slide that

NOTE Confidence: 0.9617894

00:46:17.625 --> 00:46:18.344 I showed you,

NOTE Confidence: 0.9636338

00:46:18.905 --> 00:46:20.425 fifteen minutes ago, and now

NOTE Confidence: 0.9636338

00:46:20.425 --> 00:46:22.185 putting on that the people

NOTE Confidence: 0.9636338

00:46:22.185 --> 00:46:23.645 with atherosclerotic endothelium

NOTE Confidence: 0.9172985

00:46:24.505 --> 00:46:25.965 tend to have high EC

NOTE Confidence: 0.9172985

00:46:26.025 --> 00:46:27.710 risk scores, and people with

NOTE Confidence: 0.9172985

00:46:27.710 --> 00:46:28.829 low EC risk scores, I

NOTE Confidence: 0.9172985

00:46:28.829 --> 00:46:30.430 would say, have genetically athero

NOTE Confidence: 0.9172985

00:46:30.430 --> 00:46:31.329 protective endothelium.

NOTE Confidence: 0.956179

00:46:31.710 --> 00:46:32.910 And it's really a function

NOTE Confidence: 0.956179

00:46:32.910 --> 00:46:33.869 of bear you know, the

NOTE Confidence: 0.956179

00:46:33.869 --> 00:46:35.069 the mechanisms that are driving

NOTE Confidence: 0.956179

00:46:35.069 --> 00:46:36.030 this are things that we

NOTE Confidence: 0.956179

00:46:36.030 --> 00:46:37.550 wanna study over the next

NOTE Confidence: 0.956179

00:46:37.550 --> 00:46:38.930 ten years in my lab.

NOTE Confidence: 0.937754

00:46:39.605 --> 00:46:40.565 And so with that, I'll

NOTE Confidence: 0.937754

00:46:40.565 --> 00:46:41.924 summarize sort of the approach

NOTE Confidence: 0.937754

00:46:41.924 --> 00:46:42.964 we take and then, you

NOTE Confidence: 0.937754

00:46:42.964 --> 00:46:44.184 know, leave time for questions.

NOTE Confidence: 0.9643396

00:46:44.645 --> 00:46:46.164 But I'm very excited about,

NOTE Confidence: 0.9643396

00:46:46.164 --> 00:46:47.285 like, the role of human

NOTE Confidence: 0.9643396

00:46:47.285 --> 00:46:48.565 genetics in clinical work, and

NOTE Confidence: 0.9643396

00:46:48.565 --> 00:46:50.085 I I fully admit that

NOTE Confidence: 0.9643396

00:46:50.085 --> 00:46:51.224 we've maybe

NOTE Confidence: 0.83220273

00:46:51.525 --> 00:46:52.025 overpromised

NOTE Confidence: 0.9345369

00:46:52.325 --> 00:46:54.325 and under under delivered on

NOTE Confidence: 0.9345369

00:46:54.325 --> 00:46:55.650 in some ways in certainly

NOTE Confidence: 0.9345369

00:46:55.650 --> 00:46:57.250 in cardiovascular disease. Right? We

NOTE Confidence: 0.9345369

00:46:57.250 --> 00:46:58.609 don't use clinical genetics as

NOTE Confidence: 0.9345369

00:46:58.609 --> 00:46:59.569 much as we had hoped

NOTE Confidence: 0.9345369

00:46:59.569 --> 00:47:00.469 by now.

NOTE Confidence: 0.99841243

00:47:01.170 --> 00:47:02.690 But I think that there's

NOTE Confidence: 0.99841243

00:47:02.690 --> 00:47:04.369 been two revolutions. The first

NOTE Confidence: 0.99841243

00:47:04.369 --> 00:47:05.270 is that you can

NOTE Confidence: 0.9808036

00:47:05.650 --> 00:47:06.930 identify a lot of novel

NOTE Confidence: 0.9808036

00:47:06.930 --> 00:47:09.109 variants from genome association studies.

NOTE Confidence: 0.9808036

00:47:09.170 --> 00:47:10.369 And so my lab likes

NOTE Confidence: 0.9808036

00:47:10.369 --> 00:47:11.545 to do these. We collaborate

NOTE Confidence: 0.9808036

00:47:11.545 --> 00:47:12.844 on all these big international

NOTE Confidence: 0.9808036

00:47:12.905 --> 00:47:13.405 studies

NOTE Confidence: 0.96493137

00:47:13.705 --> 00:47:15.465 to do GWAS for coronary

NOTE Confidence: 0.96493137

00:47:15.465 --> 00:47:16.364 disease and hypertension.

NOTE Confidence: 0.9763898

00:47:16.905 --> 00:47:18.665 But we're also informed by

NOTE Confidence: 0.9763898

00:47:18.665 --> 00:47:20.425 these rare diseases, thoracic or

NOTE Confidence: 0.9763898

00:47:20.425 --> 00:47:22.665 aortic disease and cerebral cavernous

NOTE Confidence: 0.9763898

00:47:22.665 --> 00:47:24.630 malformation. Those the the genes

NOTE Confidence: 0.9763898

00:47:24.630 --> 00:47:25.770 that drive those diseases

NOTE Confidence: 0.9895391

00:47:26.469 --> 00:47:26.969 overlap

NOTE Confidence: 0.99744844

00:47:27.349 --> 00:47:28.550 with the genes that drive

NOTE Confidence: 0.99744844

00:47:28.550 --> 00:47:29.450 the common diseases.

NOTE Confidence: 0.98999256

00:47:29.750 --> 00:47:31.190 And so my clinic now

NOTE Confidence: 0.98999256

00:47:31.190 --> 00:47:32.869 is almost entirely patients with

NOTE Confidence: 0.98999256

00:47:32.869 --> 00:47:34.250 cerebral cavernous malformations.

NOTE Confidence: 0.9393298

00:47:34.710 --> 00:47:35.750 And they often come see

NOTE Confidence: 0.9393298

00:47:35.750 --> 00:47:36.790 me. We'll talk for, like,

NOTE Confidence: 0.9393298

00:47:36.790 --> 00:47:37.989 forty minutes. I'll take, like,

NOTE Confidence: 0.9393298

00:47:37.989 --> 00:47:39.605 an eight generation family history,

NOTE Confidence: 0.9393298

00:47:39.825 --> 00:47:41.864 and then they'll leave and

NOTE Confidence: 0.9393298

00:47:41.864 --> 00:47:42.705 they'll say, and you're a

NOTE Confidence: 0.9393298

00:47:42.705 --> 00:47:44.065 neurosurgeon too? Because, like, that's

NOTE Confidence: 0.9393298

00:47:44.065 --> 00:47:44.785 who they're used to seeing.

NOTE Confidence: 0.9393298

00:47:44.785 --> 00:47:45.505 Right? And I'll have to

NOTE Confidence: 0.9393298

00:47:45.505 --> 00:47:46.465 apologize and say, no. No.

NOTE Confidence: 0.9393298

00:47:46.465 --> 00:47:47.265 No. I can't do anything

NOTE Confidence: 0.9393298

00:47:47.265 --> 00:47:48.385 about the lesions you have.

NOTE Confidence: 0.9393298

00:47:48.385 --> 00:47:48.885 But

NOTE Confidence: 0.9105102

00:47:49.185 --> 00:47:50.325 but mechanistically,

NOTE Confidence: 0.9773156

00:47:50.785 --> 00:47:51.905 we'll one day be able

NOTE Confidence: 0.9773156

00:47:51.905 --> 00:47:52.705 to predict who in your

NOTE Confidence: 0.9773156

00:47:52.705 --> 00:47:53.905 family is gonna have these

NOTE Confidence: 0.9773156

00:47:53.905 --> 00:47:54.405 lesions.

NOTE Confidence: 0.9724815

00:47:54.780 --> 00:47:55.500 And so,

NOTE Confidence: 0.98897743

00:47:55.980 --> 00:47:56.780 but I do think as

NOTE Confidence: 0.98897743

00:47:56.780 --> 00:47:58.460 cardiologists, right, the shared risk

NOTE Confidence: 0.98897743

00:47:58.460 --> 00:48:00.719 between seemingly unrelated vascular diseases

NOTE Confidence: 0.98897743

00:48:00.940 --> 00:48:02.380 is, like, a really powerful

NOTE Confidence: 0.98897743

00:48:02.380 --> 00:48:03.820 genetic tool and a powerful

NOTE Confidence: 0.98897743

00:48:03.820 --> 00:48:05.660 clinical tool that's very exciting

NOTE Confidence: 0.98897743

00:48:05.660 --> 00:48:07.255 to focus on. The second

NOTE Confidence: 0.98897743

00:48:07.255 --> 00:48:08.215 thing is, like, I think

NOTE Confidence: 0.98897743

00:48:08.215 --> 00:48:10.234 that every variant that's discovered

NOTE Confidence: 0.98897743

00:48:10.295 --> 00:48:11.094 should be run through one

NOTE Confidence: 0.98897743

00:48:11.094 --> 00:48:12.455 of these high throughput functional

NOTE Confidence: 0.98897743

00:48:12.455 --> 00:48:14.935 genomic screens. They're cheaper, they're

NOTE Confidence: 0.98897743

00:48:14.935 --> 00:48:16.375 accessible, and they're very fun

NOTE Confidence: 0.98897743

00:48:16.375 --> 00:48:17.655 to use. Right? You instead

NOTE Confidence: 0.98897743

00:48:17.655 --> 00:48:19.094 of picking an individual variant

NOTE Confidence: 0.98897743

00:48:19.094 --> 00:48:20.055 and hoping it has an

NOTE Confidence: 0.98897743

00:48:20.055 --> 00:48:21.820 effect, you study the effect

NOTE Confidence: 0.98897743

00:48:21.820 --> 00:48:23.020 of every variant in the

NOTE Confidence: 0.98897743

00:48:23.020 --> 00:48:24.380 genome and only study the

NOTE Confidence: 0.98897743

00:48:24.380 --> 00:48:25.500 ones that have the strongest

NOTE Confidence: 0.98897743

00:48:25.500 --> 00:48:26.000 effect.

NOTE Confidence: 0.96806073

00:48:26.300 --> 00:48:27.500 We never would have picked

NOTE Confidence: 0.96806073

00:48:27.500 --> 00:48:29.119 to study the CCM pathway

NOTE Confidence: 0.96806073

00:48:29.180 --> 00:48:30.380 if we were just randomly

NOTE Confidence: 0.96806073

00:48:30.380 --> 00:48:31.820 picking variants because those genes

NOTE Confidence: 0.96806073

00:48:31.820 --> 00:48:32.480 are ubiquitously

NOTE Confidence: 0.9866073

00:48:32.825 --> 00:48:34.265 expressed in every cell type.

NOTE Confidence: 0.9866073

00:48:34.265 --> 00:48:35.465 There's nothing about them that's

NOTE Confidence: 0.9866073

00:48:35.465 --> 00:48:36.845 endothelial cell specific,

NOTE Confidence: 0.9664902

00:48:37.225 --> 00:48:38.745 but the diseases associated with

NOTE Confidence: 0.9664902

00:48:38.745 --> 00:48:39.945 those variants are only in

NOTE Confidence: 0.9664902

00:48:39.945 --> 00:48:42.285 endothelial cells, interestingly enough.

NOTE Confidence: 0.99686575

00:48:42.745 --> 00:48:43.705 And what we hope is

NOTE Confidence: 0.99686575

00:48:43.705 --> 00:48:45.405 that instead of, like, identifying

NOTE Confidence: 0.9765256

00:48:45.705 --> 00:48:47.225 specific variants that are worth

NOTE Confidence: 0.9765256

00:48:47.225 --> 00:48:49.340 studying, we'll find causal genes

NOTE Confidence: 0.9765256

00:48:49.340 --> 00:48:51.020 and risk pathways for vascular

NOTE Confidence: 0.9765256

00:48:51.020 --> 00:48:51.900 disease. And that's sort of

NOTE Confidence: 0.9765256

00:48:51.900 --> 00:48:53.980 the the the the output

NOTE Confidence: 0.9765256

00:48:53.980 --> 00:48:55.200 of our work so far.

NOTE Confidence: 0.9765256

00:48:55.260 --> 00:48:56.140 And so I've I've sort

NOTE Confidence: 0.9765256

00:48:56.140 --> 00:48:57.500 of gone over all these

NOTE Confidence: 0.9765256

00:48:57.500 --> 00:48:58.540 these things that, you know,

NOTE Confidence: 0.9765256

00:48:58.540 --> 00:49:00.160 we find co regulated programs.

NOTE Confidence: 0.9765256

00:49:00.455 --> 00:49:01.435 We find shared mechanisms

NOTE Confidence: 0.9751501

00:49:01.735 --> 00:49:03.094 of disease. I think this

NOTE Confidence: 0.9751501

00:49:03.094 --> 00:49:04.875 endothelial cell risk score identifies

NOTE Confidence: 0.9751501

00:49:05.015 --> 00:49:06.635 unique mechanisms of risk,

NOTE Confidence: 0.93308043

00:49:06.935 --> 00:49:08.455 and it identifies the patients

NOTE Confidence: 0.93308043

00:49:08.455 --> 00:49:09.815 with the strongest response to

NOTE Confidence: 0.93308043

00:49:09.815 --> 00:49:11.415 lipid lowering therapies. And just

NOTE Confidence: 0.93308043

00:49:11.415 --> 00:49:12.935 to preempt a question from

NOTE Confidence: 0.93308043

00:49:12.935 --> 00:49:13.975 a student clinician in the

NOTE Confidence: 0.93308043

00:49:13.975 --> 00:49:15.370 audience. Right? So then would

NOTE Confidence: 0.93308043

00:49:15.370 --> 00:49:16.650 you say that really the

NOTE Confidence: 0.93308043

00:49:16.650 --> 00:49:17.710 endothelial cell,

NOTE Confidence: 0.97678375

00:49:18.170 --> 00:49:19.450 risk score just says we

NOTE Confidence: 0.97678375

00:49:19.450 --> 00:49:21.310 should start statins earlier. Right?

NOTE Confidence: 0.97678375

00:49:21.609 --> 00:49:22.989 And, yes, in this population,

NOTE Confidence: 0.97678375

00:49:23.050 --> 00:49:24.010 these are the people who

NOTE Confidence: 0.97678375

00:49:24.010 --> 00:49:25.050 you might start statins in

NOTE Confidence: 0.97678375

00:49:25.050 --> 00:49:26.010 when they were when they're

NOTE Confidence: 0.97678375

00:49:26.010 --> 00:49:27.369 in their twenties or thirties.

NOTE Confidence: 0.97678375

00:49:27.369 --> 00:49:28.330 Right? Because they're the ones

NOTE Confidence: 0.97678375

00:49:28.330 --> 00:49:30.055 who are driving greatest benefit

NOTE Confidence: 0.97678375

00:49:30.055 --> 00:49:31.415 from statins, and these are

NOTE Confidence: 0.97678375

00:49:31.415 --> 00:49:32.375 the patients who have the

NOTE Confidence: 0.97678375

00:49:32.375 --> 00:49:34.235 highest toxicity from high LDL.

NOTE Confidence: 0.975614

00:49:35.094 --> 00:49:36.535 But also, the truth is

NOTE Confidence: 0.975614

00:49:36.535 --> 00:49:37.895 that as cardiologists, right, we

NOTE Confidence: 0.975614

00:49:37.895 --> 00:49:39.335 only start treating patients when

NOTE Confidence: 0.975614

00:49:39.335 --> 00:49:40.455 they've had their first heart

NOTE Confidence: 0.975614

00:49:40.455 --> 00:49:42.055 attack. Right? Prevention is never

NOTE Confidence: 0.975614

00:49:42.055 --> 00:49:43.415 gonna catch up to secondary

NOTE Confidence: 0.975614

00:49:43.415 --> 00:49:43.915 prevention.

NOTE Confidence: 0.9799034

00:49:44.349 --> 00:49:46.109 And so once you're treating

NOTE Confidence: 0.9799034

00:49:46.109 --> 00:49:47.070 a patient who's already had

NOTE Confidence: 0.9799034

00:49:47.070 --> 00:49:48.109 a heart attack, you sort

NOTE Confidence: 0.9799034

00:49:48.109 --> 00:49:48.750 of have to throw the

NOTE Confidence: 0.9799034

00:49:48.750 --> 00:49:50.030 kitchen sink at them. And

NOTE Confidence: 0.9799034

00:49:50.030 --> 00:49:51.170 that would be the motivation

NOTE Confidence: 0.9799034

00:49:51.390 --> 00:49:53.550 for having targeted therapies for

NOTE Confidence: 0.9799034

00:49:53.550 --> 00:49:55.230 this pathway as well. And

NOTE Confidence: 0.9799034

00:49:55.230 --> 00:49:56.349 then I'll I'll put in

NOTE Confidence: 0.9799034

00:49:56.349 --> 00:49:57.550 my sort of my my

NOTE Confidence: 0.9799034

00:49:57.550 --> 00:49:59.295 my plug that I think

NOTE Confidence: 0.9799034

00:49:59.295 --> 00:50:01.614 precision medicine will ultimately be,

NOTE Confidence: 0.9799034

00:50:01.614 --> 00:50:02.734 you know, at that intersection

NOTE Confidence: 0.9799034

00:50:02.734 --> 00:50:04.435 of of genetics and function.

NOTE Confidence: 0.9705265

00:50:05.055 --> 00:50:06.255 And so with that, I'll

NOTE Confidence: 0.9705265

00:50:06.255 --> 00:50:07.714 thank, you know, the the

NOTE Confidence: 0.9705265

00:50:07.775 --> 00:50:08.895 great members of my lab

NOTE Confidence: 0.9705265

00:50:08.895 --> 00:50:09.775 who've done all this work.

NOTE Confidence: 0.9705265

00:50:09.775 --> 00:50:11.155 I have wonderful collaborators.

NOTE Confidence: 0.98681736

00:50:11.910 --> 00:50:12.410 And,

NOTE Confidence: 0.97913677

00:50:12.869 --> 00:50:14.230 and I'll just end by

NOTE Confidence: 0.97913677

00:50:14.230 --> 00:50:15.030 saying that, you know you

NOTE Confidence: 0.97913677

00:50:15.030 --> 00:50:16.069 know, presenting here is, you

NOTE Confidence: 0.97913677

00:50:16.069 --> 00:50:17.290 know, been a real pleasure

NOTE Confidence: 0.97913677

00:50:17.349 --> 00:50:18.150 in front of a great

NOTE Confidence: 0.97913677

00:50:18.150 --> 00:50:19.750 audience, and, I'm excited to

NOTE Confidence: 0.97913677

00:50:19.750 --> 00:50:20.790 answer any questions you all

NOTE Confidence: 0.97913677

00:50:20.790 --> 00:50:21.290 have.

NOTE Confidence: 0.89934224

00:50:31.775 --> 00:50:33.214 Is there any questions in

NOTE Confidence: 0.89934224

00:50:33.214 --> 00:50:33.954 the audience?

NOTE Confidence: 0.8895352

00:50:37.310 --> 00:50:38.670 Have that back, and then

NOTE Confidence: 0.8895352

00:50:38.670 --> 00:50:39.650 I'll come back to

NOTE Confidence: 0.85966957

00:50:41.469 --> 00:50:41.969 John.

NOTE Confidence: 0.93933624

00:50:43.950 --> 00:50:44.930 Raj, that was

NOTE Confidence: 0.99212587

00:50:46.190 --> 00:50:47.410 Raj, that was awesome.

NOTE Confidence: 0.9684942

00:50:48.670 --> 00:50:49.245 I guess,

NOTE Confidence: 0.9488368

00:50:49.805 --> 00:50:51.645 a first question is if

NOTE Confidence: 0.9488368

00:50:51.645 --> 00:50:53.885 your polygenic risk score personally

NOTE Confidence: 0.9488368

00:50:53.885 --> 00:50:54.845 was higher for a different

NOTE Confidence: 0.9488368

00:50:54.845 --> 00:50:55.965 disease, would you be studying

NOTE Confidence: 0.9488368

00:50:55.965 --> 00:50:56.865 a different disease?

NOTE Confidence: 0.9787763

00:50:58.765 --> 00:51:00.045 Right. Yeah. Yeah. Exactly. I

NOTE Confidence: 0.9787763

00:51:00.045 --> 00:51:00.925 I got lucky that it

NOTE Confidence: 0.9787763

00:51:00.925 --> 00:51:02.045 was because I was already

NOTE Confidence: 0.9787763

00:51:02.045 --> 00:51:03.085 studying. Right? I guess you

NOTE Confidence: 0.9787763

00:51:03.085 --> 00:51:03.905 could say that.

NOTE Confidence: 0.84402186

00:51:04.489 --> 00:51:05.690 Yeah. No. I I definitely

NOTE Confidence: 0.84402186

00:51:05.690 --> 00:51:06.809 would probably that, yeah, I've

NOTE Confidence: 0.84402186

00:51:06.809 --> 00:51:08.030 been studying something else.

NOTE Confidence: 0.9082947

00:51:08.569 --> 00:51:09.069 So

NOTE Confidence: 0.9590952

00:51:10.010 --> 00:51:10.969 I guess I have a

NOTE Confidence: 0.9590952

00:51:10.969 --> 00:51:11.849 a number of questions, but

NOTE Confidence: 0.9590952

00:51:11.849 --> 00:51:12.730 I'll I'll stick with this.

NOTE Confidence: 0.9590952

00:51:12.730 --> 00:51:13.210 So,

NOTE Confidence: 0.9785138

00:51:15.290 --> 00:51:16.989 you know, it it's fascinating

NOTE Confidence: 0.9785138

00:51:17.130 --> 00:51:18.030 that the endothelial

NOTE Confidence: 0.94400865

00:51:18.489 --> 00:51:20.565 risk score, how it's interrelating

NOTE Confidence: 0.94400865

00:51:20.705 --> 00:51:21.205 with,

NOTE Confidence: 0.9209358

00:51:21.825 --> 00:51:24.165 LDL cholesterol with high cholesterol.

NOTE Confidence: 0.99563944

00:51:24.864 --> 00:51:26.805 What about with, other therapies

NOTE Confidence: 0.99563944

00:51:26.864 --> 00:51:28.965 for atherosclerosis? What about antihypertension?

NOTE Confidence: 0.9970396

00:51:29.265 --> 00:51:30.165 What about aspirin?

NOTE Confidence: 0.94654727

00:51:31.105 --> 00:51:32.645 Does that also predict them?

NOTE Confidence: 0.94654727

00:51:32.840 --> 00:51:34.600 Yeah. So sadly. Right? Like,

NOTE Confidence: 0.94654727

00:51:34.600 --> 00:51:35.560 we have access to the

NOTE Confidence: 0.94654727

00:51:35.560 --> 00:51:37.239 LDL data because it it

NOTE Confidence: 0.94654727

00:51:37.239 --> 00:51:38.600 was, you know, done as

NOTE Confidence: 0.94654727

00:51:38.600 --> 00:51:39.500 clinical trials.

NOTE Confidence: 0.96981066

00:51:40.200 --> 00:51:41.719 And therapies for aspirin and

NOTE Confidence: 0.96981066

00:51:41.719 --> 00:51:43.640 hypertension didn't genotype right at

NOTE Confidence: 0.96981066

00:51:43.640 --> 00:51:44.520 the time. So we don't

NOTE Confidence: 0.96981066

00:51:44.520 --> 00:51:46.380 have genomic information on that.

NOTE Confidence: 0.9993467

00:51:47.065 --> 00:51:48.045 I would predict

NOTE Confidence: 0.9845203

00:51:48.425 --> 00:51:49.225 that it would be even

NOTE Confidence: 0.9845203

00:51:49.225 --> 00:51:50.525 stronger for antihypertensive

NOTE Confidence: 0.9376426

00:51:51.225 --> 00:51:53.325 therapies, or for even aspirin,

NOTE Confidence: 0.87723416

00:51:53.785 --> 00:51:54.905 or, you know, maybe even

NOTE Confidence: 0.87723416

00:51:54.905 --> 00:51:56.825 in anti inflammatory therapies would

NOTE Confidence: 0.87723416

00:51:56.825 --> 00:51:58.205 have would have a a

NOTE Confidence: 0.87723416

00:51:58.425 --> 00:52:00.364 a a correlation as well.

NOTE Confidence: 0.87723416

00:52:00.585 --> 00:52:00.825 But,

NOTE Confidence: 0.9752579

00:52:01.969 --> 00:52:03.410 we don't have genomic information.

NOTE Confidence: 0.9752579

00:52:03.410 --> 00:52:04.769 We're we tried to get

NOTE Confidence: 0.9752579

00:52:04.769 --> 00:52:06.390 access to CANTOS, and Novartis

NOTE Confidence: 0.9752579

00:52:06.450 --> 00:52:07.650 did not allow it. Right?

NOTE Confidence: 0.9752579

00:52:07.809 --> 00:52:08.930 Because they were still doing

NOTE Confidence: 0.9752579

00:52:08.930 --> 00:52:10.450 the clinical trial for lung

NOTE Confidence: 0.9752579

00:52:10.450 --> 00:52:10.950 cancer.

NOTE Confidence: 0.95307904

00:52:11.250 --> 00:52:12.369 And, you know, they didn't

NOTE Confidence: 0.95307904

00:52:12.369 --> 00:52:13.809 wanna, like, kinda change the

NOTE Confidence: 0.95307904

00:52:13.809 --> 00:52:14.930 the story that was coming

NOTE Confidence: 0.95307904

00:52:14.930 --> 00:52:15.954 out for those anti l

NOTE Confidence: 0.95307904

00:52:15.954 --> 00:52:17.795 one beta therapies. But, it's

NOTE Confidence: 0.95307904

00:52:17.795 --> 00:52:18.935 just a lack of data.

NOTE Confidence: 0.9309631

00:52:19.315 --> 00:52:20.355 The reason we haven't studied

NOTE Confidence: 0.9309631

00:52:20.355 --> 00:52:21.555 that. And then doing small

NOTE Confidence: 0.9309631

00:52:21.555 --> 00:52:22.515 follow-up. So do you think

NOTE Confidence: 0.9309631

00:52:22.515 --> 00:52:24.135 the the effect then,

NOTE Confidence: 0.97339445

00:52:25.795 --> 00:52:27.474 based on the LDL level

NOTE Confidence: 0.97339445

00:52:27.474 --> 00:52:28.935 of the statin is independent

NOTE Confidence: 0.97339445

00:52:29.155 --> 00:52:31.440 then of its anti cholesterol?

NOTE Confidence: 0.97339445

00:52:31.440 --> 00:52:32.160 Do you think it's more

NOTE Confidence: 0.97339445

00:52:32.160 --> 00:52:34.000 of an anti inflammatory effect?

NOTE Confidence: 0.97339445

00:52:34.000 --> 00:52:35.680 Or Right. Yeah. Yeah. So,

NOTE Confidence: 0.9608348

00:52:36.080 --> 00:52:36.800 right. Like, one of the

NOTE Confidence: 0.9608348

00:52:36.800 --> 00:52:37.920 effects of statins is that

NOTE Confidence: 0.9608348

00:52:37.920 --> 00:52:39.520 it raises KLF two, which

NOTE Confidence: 0.9608348

00:52:39.520 --> 00:52:40.880 is that forty that the

NOTE Confidence: 0.9608348

00:52:40.880 --> 00:52:41.840 forty one genes are in

NOTE Confidence: 0.9608348

00:52:41.840 --> 00:52:43.540 that KLF two regulatory pathway.

NOTE Confidence: 0.97101355

00:52:43.844 --> 00:52:45.285 And so maybe there's a

NOTE Confidence: 0.97101355

00:52:45.285 --> 00:52:46.724 direct effect of the stat

NOTE Confidence: 0.97101355

00:52:46.724 --> 00:52:48.005 that's protective. But then we

NOTE Confidence: 0.97101355

00:52:48.005 --> 00:52:49.385 looked at PCSK nine inhibitors,

NOTE Confidence: 0.97101355

00:52:49.445 --> 00:52:50.484 which don't have that Klf

NOTE Confidence: 0.97101355

00:52:50.484 --> 00:52:51.205 two effect, and it was

NOTE Confidence: 0.97101355

00:52:51.205 --> 00:52:52.585 the almost the same association.

NOTE Confidence: 0.9914748

00:52:53.285 --> 00:52:55.305 And so I think that

NOTE Confidence: 0.9914748

00:52:55.364 --> 00:52:57.065 it's probably minimally

NOTE Confidence: 0.9809586

00:52:58.560 --> 00:53:00.000 the, the the direct effect

NOTE Confidence: 0.9809586

00:53:00.000 --> 00:53:01.440 of the drug, and it's

NOTE Confidence: 0.9809586

00:53:01.440 --> 00:53:03.540 more the toxicity of LDL

NOTE Confidence: 0.9766765

00:53:04.080 --> 00:53:05.780 in patients with dysfunctional endothelial

NOTE Confidence: 0.9766765

00:53:05.920 --> 00:53:07.520 cells. That that it's just

NOTE Confidence: 0.9766765

00:53:07.520 --> 00:53:09.860 that bad endothelial cells predisposed

NOTE Confidence: 0.9766765

00:53:10.000 --> 00:53:10.900 to plaque formation.

NOTE Confidence: 0.99373543

00:53:11.435 --> 00:53:12.315 And when we think about

NOTE Confidence: 0.99373543

00:53:12.315 --> 00:53:13.535 it, like, you know, what

NOTE Confidence: 0.9531799

00:53:14.155 --> 00:53:15.275 is, who are the people

NOTE Confidence: 0.9531799

00:53:15.275 --> 00:53:16.555 who are resilient to coronary

NOTE Confidence: 0.9531799

00:53:16.555 --> 00:53:17.594 disease? Right? The patients you

NOTE Confidence: 0.9531799

00:53:17.594 --> 00:53:19.114 have who smoked for fifty

NOTE Confidence: 0.9531799

00:53:19.114 --> 00:53:20.655 years or had hypertension

NOTE Confidence: 0.9485993

00:53:21.195 --> 00:53:22.075 or, you know, even your

NOTE Confidence: 0.9485993

00:53:22.075 --> 00:53:23.055 familial hypercholesterols

NOTE Confidence: 0.9704946

00:53:24.420 --> 00:53:25.540 FH patients who never get

NOTE Confidence: 0.9704946

00:53:25.540 --> 00:53:26.579 coronary disease. There are some

NOTE Confidence: 0.9704946

00:53:26.579 --> 00:53:27.700 people like that. They must

NOTE Confidence: 0.9704946

00:53:27.700 --> 00:53:29.160 have some endothelial resilience.

NOTE Confidence: 0.96503186

00:53:29.700 --> 00:53:30.900 And so I think this

NOTE Confidence: 0.96503186

00:53:30.900 --> 00:53:32.099 this polygenic risk score would

NOTE Confidence: 0.96503186

00:53:32.099 --> 00:53:33.940 probably capture some component of

NOTE Confidence: 0.96503186

00:53:33.940 --> 00:53:34.440 that.

NOTE Confidence: 0.9877796

00:53:38.605 --> 00:53:40.465 That was an awesome talk.

NOTE Confidence: 0.61355543

00:53:42.125 --> 00:53:42.205 And,

NOTE Confidence: 0.9926237

00:53:43.725 --> 00:53:45.485 as a vascular biologist, I

NOTE Confidence: 0.9926237

00:53:45.485 --> 00:53:47.425 like your endothelial cell centric

NOTE Confidence: 0.9926237

00:53:47.565 --> 00:53:49.405 approach to risk scores. I

NOTE Confidence: 0.9926237

00:53:49.405 --> 00:53:50.625 I think that's terrific.

NOTE Confidence: 0.87181604

00:53:51.620 --> 00:53:52.120 But,

NOTE Confidence: 0.99917126

00:53:52.660 --> 00:53:53.540 one thing I would say

NOTE Confidence: 0.99917126

00:53:53.540 --> 00:53:54.040 is

NOTE Confidence: 0.95684737

00:53:54.420 --> 00:53:55.940 I remember about fifteen years

NOTE Confidence: 0.95684737

00:53:55.940 --> 00:53:57.380 ago, maybe even a little

NOTE Confidence: 0.95684737

00:53:57.380 --> 00:53:59.380 bit more, Joe Lascalso put

NOTE Confidence: 0.95684737

00:53:59.380 --> 00:54:01.480 a slide up, at a

NOTE Confidence: 0.9639699

00:54:01.940 --> 00:54:03.380 small scientific meeting, and it

NOTE Confidence: 0.9639699

00:54:03.380 --> 00:54:04.900 was one and you've probably

NOTE Confidence: 0.9639699

00:54:04.900 --> 00:54:06.135 seen him do this. It

NOTE Confidence: 0.9639699

00:54:06.135 --> 00:54:07.035 was one of

NOTE Confidence: 0.9991351

00:54:07.575 --> 00:54:08.715 those very complicated

NOTE Confidence: 0.91599756

00:54:09.335 --> 00:54:10.395 system circuitry

NOTE Confidence: 0.9953647

00:54:10.695 --> 00:54:11.594 slides with

NOTE Confidence: 0.95779777

00:54:12.455 --> 00:54:14.135 four hundred arrows going in

NOTE Confidence: 0.95779777

00:54:14.135 --> 00:54:15.435 lots of different directions.

NOTE Confidence: 0.96388537

00:54:15.735 --> 00:54:16.715 And he said,

NOTE Confidence: 0.99034107

00:54:17.015 --> 00:54:18.295 a human being is not

NOTE Confidence: 0.99034107

00:54:18.295 --> 00:54:19.515 an inbred mass.

NOTE Confidence: 0.984891

00:54:20.160 --> 00:54:21.920 So you all are knocking

NOTE Confidence: 0.984891

00:54:21.920 --> 00:54:24.099 out genes in inbred animals,

NOTE Confidence: 0.984891

00:54:24.160 --> 00:54:25.680 and there's so many gene

NOTE Confidence: 0.984891

00:54:25.680 --> 00:54:27.599 gene interactions and gene gene

NOTE Confidence: 0.984891

00:54:27.599 --> 00:54:28.099 modifiers.

NOTE Confidence: 0.95645994

00:54:29.040 --> 00:54:30.640 And so I guess, you

NOTE Confidence: 0.95645994

00:54:30.640 --> 00:54:31.760 know, I'm trying not to

NOTE Confidence: 0.95645994

00:54:31.760 --> 00:54:32.799 make this too long a

NOTE Confidence: 0.95645994

00:54:32.799 --> 00:54:34.875 question, but it gets to

NOTE Confidence: 0.95645994

00:54:34.875 --> 00:54:37.055 the point of even your

NOTE Confidence: 0.95645994

00:54:37.114 --> 00:54:38.555 risk scores based on a

NOTE Confidence: 0.95645994

00:54:38.555 --> 00:54:40.235 set of genes, right, that

NOTE Confidence: 0.95645994

00:54:40.235 --> 00:54:42.155 you define, which is beautiful

NOTE Confidence: 0.95645994

00:54:42.155 --> 00:54:43.215 work and incredible.

NOTE Confidence: 0.9006424

00:54:43.755 --> 00:54:45.435 But are we ever gonna

NOTE Confidence: 0.9006424

00:54:45.435 --> 00:54:47.035 get there until we are

NOTE Confidence: 0.9006424

00:54:47.035 --> 00:54:47.155 able to have this incredibly

NOTE Confidence: 0.9006424

00:54:47.155 --> 00:54:47.275 complicated scorecard where everything goes

NOTE Confidence: 0.9006424

00:54:47.275 --> 00:54:47.775 into

NOTE Confidence: 0.19475588

00:54:48.795 --> 00:54:49.295 the

NOTE Confidence: 0.957573

00:54:59.480 --> 00:55:01.320 variants that are identified are

NOTE Confidence: 0.957573

00:55:01.320 --> 00:55:01.820 noncoding

NOTE Confidence: 0.99585354

00:55:02.120 --> 00:55:02.620 regions.

NOTE Confidence: 0.9194062

00:55:03.015 --> 00:55:04.154 A lot of those noncoding

NOTE Confidence: 0.9194062

00:55:04.214 --> 00:55:05.414 regions you know better than

NOTE Confidence: 0.9194062

00:55:05.414 --> 00:55:05.994 I do

NOTE Confidence: 0.9686649

00:55:06.375 --> 00:55:07.194 are influential

NOTE Confidence: 0.96476185

00:55:07.815 --> 00:55:08.855 in a lot of different

NOTE Confidence: 0.96476185

00:55:08.855 --> 00:55:10.555 ways. I mean, interchromosomal

NOTE Confidence: 0.9975754

00:55:11.174 --> 00:55:11.674 interactions,

NOTE Confidence: 0.99750245

00:55:13.094 --> 00:55:13.594 epigenetics

NOTE Confidence: 0.9986914

00:55:13.974 --> 00:55:15.035 based on sequence,

NOTE Confidence: 0.97327375

00:55:15.335 --> 00:55:17.275 noncoding RNAs, etcetera, etcetera.

NOTE Confidence: 0.99830985

00:55:17.815 --> 00:55:18.315 So

NOTE Confidence: 0.99612886

00:55:18.830 --> 00:55:20.070 how do you think about

NOTE Confidence: 0.99612886

00:55:20.270 --> 00:55:21.810 Yeah. The noncoding

NOTE Confidence: 0.97471255

00:55:22.190 --> 00:55:23.790 sequence, and what about this

NOTE Confidence: 0.97471255

00:55:23.790 --> 00:55:24.850 very complicated

NOTE Confidence: 0.9497232

00:55:25.310 --> 00:55:26.830 Yeah. Process? Right. Right. Yeah.

NOTE Confidence: 0.9497232

00:55:26.830 --> 00:55:28.030 So I completely agree that,

NOTE Confidence: 0.9497232

00:55:28.030 --> 00:55:28.830 like, you know,

NOTE Confidence: 0.9971194

00:55:29.310 --> 00:55:30.110 this is all,

NOTE Confidence: 0.9936539

00:55:30.430 --> 00:55:31.489 you know, a reductionist

NOTE Confidence: 0.9338232

00:55:31.790 --> 00:55:33.150 sort of lens on a

NOTE Confidence: 0.9338232

00:55:33.150 --> 00:55:34.435 systems problem.

NOTE Confidence: 0.9959979

00:55:35.055 --> 00:55:36.835 And I'm telling you, like,

NOTE Confidence: 0.97413695

00:55:37.215 --> 00:55:37.715 one,

NOTE Confidence: 0.9820486

00:55:38.494 --> 00:55:39.935 conclusion from our data is

NOTE Confidence: 0.9820486

00:55:39.935 --> 00:55:41.295 that, oh, there's this direct

NOTE Confidence: 0.9820486

00:55:41.295 --> 00:55:43.215 interaction between LDL and endothelial

NOTE Confidence: 0.9820486

00:55:43.215 --> 00:55:45.055 cells. But an alternative theory

NOTE Confidence: 0.9820486

00:55:45.055 --> 00:55:45.775 is that, you know, these

NOTE Confidence: 0.9820486

00:55:45.775 --> 00:55:46.494 are just this is just

NOTE Confidence: 0.9820486

00:55:46.494 --> 00:55:48.130 a complex system. And if

NOTE Confidence: 0.9820486

00:55:48.130 --> 00:55:49.489 it's perturbed in any way,

NOTE Confidence: 0.9820486

00:55:49.489 --> 00:55:51.010 you're gonna see additive effects.

NOTE Confidence: 0.9820486

00:55:51.010 --> 00:55:51.890 And I'm just looking at

NOTE Confidence: 0.9820486

00:55:51.890 --> 00:55:52.550 two different

NOTE Confidence: 0.99378407

00:55:52.850 --> 00:55:54.390 parts of the system diagram.

NOTE Confidence: 0.9596158

00:55:55.090 --> 00:55:56.370 And, it would be the

NOTE Confidence: 0.9596158

00:55:56.370 --> 00:55:57.330 same if I had an,

NOTE Confidence: 0.9596158

00:55:57.730 --> 00:55:59.105 inflammation risk score, and it'd

NOTE Confidence: 0.9596158

00:55:59.105 --> 00:55:59.744 be the same if I

NOTE Confidence: 0.9596158

00:55:59.744 --> 00:56:01.105 had a vascular muscle risk

NOTE Confidence: 0.9596158

00:56:01.105 --> 00:56:02.385 score. And so we we'd

NOTE Confidence: 0.9596158

00:56:02.385 --> 00:56:03.905 have to investigate that. So

NOTE Confidence: 0.9596158

00:56:03.905 --> 00:56:05.265 I I think we're trying

NOTE Confidence: 0.9596158

00:56:05.265 --> 00:56:06.305 to build those things, and

NOTE Confidence: 0.9596158

00:56:06.305 --> 00:56:07.105 and, you know, the right

NOTE Confidence: 0.9596158

00:56:07.105 --> 00:56:08.385 set of controls don't exist

NOTE Confidence: 0.9596158

00:56:08.385 --> 00:56:09.765 to really answer your question.

NOTE Confidence: 0.97362137

00:56:10.065 --> 00:56:11.505 As far as noncoding. Right?

NOTE Confidence: 0.97362137

00:56:11.505 --> 00:56:11.744 So,

NOTE Confidence: 0.9585754

00:56:12.700 --> 00:56:14.219 you know, we're trying to

NOTE Confidence: 0.9585754

00:56:14.219 --> 00:56:15.980 actually identify the causal genes

NOTE Confidence: 0.9585754

00:56:15.980 --> 00:56:17.600 using this perturb seek method.

NOTE Confidence: 0.9585754

00:56:17.820 --> 00:56:18.940 But your point is that,

NOTE Confidence: 0.9585754

00:56:18.940 --> 00:56:20.800 you know, that's still assuming

NOTE Confidence: 0.9585754

00:56:20.860 --> 00:56:22.140 that it's just one gene,

NOTE Confidence: 0.9585754

00:56:22.140 --> 00:56:23.660 one effect for risk variant,

NOTE Confidence: 0.9585754

00:56:23.660 --> 00:56:24.800 but maybe the risk variants

NOTE Confidence: 0.9585754

00:56:25.020 --> 00:56:26.515 have different functions in different

NOTE Confidence: 0.9585754

00:56:26.515 --> 00:56:27.575 stages of disease.

NOTE Confidence: 0.94403225

00:56:27.875 --> 00:56:29.155 Maybe they have different functions

NOTE Confidence: 0.94403225

00:56:29.155 --> 00:56:30.435 in different cells at each

NOTE Confidence: 0.94403225

00:56:30.435 --> 00:56:31.475 stage of disease and that

NOTE Confidence: 0.94403225

00:56:31.475 --> 00:56:32.835 we cannot model in a

NOTE Confidence: 0.94403225

00:56:32.835 --> 00:56:33.955 dish. So I've I've sort

NOTE Confidence: 0.94403225

00:56:33.955 --> 00:56:35.235 of told people that, you

NOTE Confidence: 0.94403225

00:56:35.235 --> 00:56:36.195 know, we just got this

NOTE Confidence: 0.94403225

00:56:36.195 --> 00:56:37.715 PPG to do in vivo

NOTE Confidence: 0.94403225

00:56:37.715 --> 00:56:38.675 for TRP seq where we

NOTE Confidence: 0.94403225

00:56:38.675 --> 00:56:39.975 can take a a CRISPRi

NOTE Confidence: 0.94403225

00:56:40.114 --> 00:56:40.614 mouse,

NOTE Confidence: 0.9780472

00:56:41.319 --> 00:56:42.680 inject the same guide RNA

NOTE Confidence: 0.9780472

00:56:42.680 --> 00:56:43.799 library, and then do single

NOTE Confidence: 0.9780472

00:56:43.799 --> 00:56:45.319 cell RNA sequencing of the

NOTE Confidence: 0.9780472

00:56:45.319 --> 00:56:46.760 different cell types that got

NOTE Confidence: 0.9780472

00:56:46.760 --> 00:56:48.280 the the guides. And then,

NOTE Confidence: 0.9780472

00:56:48.280 --> 00:56:49.319 you know, the criticism of

NOTE Confidence: 0.9780472

00:56:49.319 --> 00:56:50.119 the work I've done is

NOTE Confidence: 0.9780472

00:56:50.119 --> 00:56:51.000 that it's just some cells

NOTE Confidence: 0.9780472

00:56:51.000 --> 00:56:52.760 in a dish, but now

NOTE Confidence: 0.9780472

00:56:52.760 --> 00:56:54.119 we can really do this,

NOTE Confidence: 0.9780472

00:56:54.119 --> 00:56:55.339 you know, in a systems

NOTE Confidence: 0.87215745

00:56:55.640 --> 00:56:56.140 system.

NOTE Confidence: 0.76872456

00:56:56.440 --> 00:56:56.940 Yes.

NOTE Confidence: 0.9575765

00:56:58.015 --> 00:56:59.295 That was a great talk.

NOTE Confidence: 0.9575765

00:56:59.295 --> 00:57:00.895 And my question is in

NOTE Confidence: 0.9575765

00:57:00.895 --> 00:57:01.395 some

NOTE Confidence: 0.8433216

00:57:01.695 --> 00:57:02.594 in some degree

NOTE Confidence: 0.9424305

00:57:02.975 --> 00:57:04.755 relates to Jeff's question also.

NOTE Confidence: 0.99895644

00:57:05.535 --> 00:57:06.675 So you

NOTE Confidence: 0.9995346

00:57:06.975 --> 00:57:07.475 are

NOTE Confidence: 0.9978316

00:57:07.855 --> 00:57:08.835 we talked about,

NOTE Confidence: 0.9279532

00:57:09.455 --> 00:57:10.915 implications for therapy.

NOTE Confidence: 0.99406445

00:57:11.660 --> 00:57:12.620 And I was looking at

NOTE Confidence: 0.99406445

00:57:12.620 --> 00:57:13.980 the graphs and prevalence of

NOTE Confidence: 0.99406445

00:57:13.980 --> 00:57:15.180 disease that we were talking

NOTE Confidence: 0.99406445

00:57:15.180 --> 00:57:16.220 about over a ten year

NOTE Confidence: 0.99406445

00:57:16.220 --> 00:57:16.720 period.

NOTE Confidence: 0.9323559

00:57:17.260 --> 00:57:19.280 What's the predictive positive predictive

NOTE Confidence: 0.9323559

00:57:19.340 --> 00:57:21.200 value of this this polygenic

NOTE Confidence: 0.9323559

00:57:21.340 --> 00:57:23.360 risk scores, whether it's lipid

NOTE Confidence: 0.99403167

00:57:23.755 --> 00:57:24.494 or endothelial

NOTE Confidence: 0.92955905

00:57:24.795 --> 00:57:26.234 because we're going to apply

NOTE Confidence: 0.92955905

00:57:26.234 --> 00:57:27.915 them to individual patients, not

NOTE Confidence: 0.92955905

00:57:27.915 --> 00:57:29.135 to a population.

NOTE Confidence: 0.98349285

00:57:29.994 --> 00:57:31.195 Right. Right. Yeah. So it's

NOTE Confidence: 0.98349285

00:57:31.195 --> 00:57:32.715 small. Right? So the the

NOTE Confidence: 0.98349285

00:57:32.715 --> 00:57:33.994 positive predictive value of, like

NOTE Confidence: 0.98349285

00:57:34.155 --> 00:57:35.695 so someone at the top,

NOTE Confidence: 0.94793457

00:57:36.950 --> 00:57:38.470 the top range of polygenic

NOTE Confidence: 0.94793457

00:57:38.470 --> 00:57:40.550 risk score has about two

NOTE Confidence: 0.94793457

00:57:40.550 --> 00:57:42.090 to five fold higher risk.

NOTE Confidence: 0.94793457

00:57:42.310 --> 00:57:43.910 Okay? And then it it

NOTE Confidence: 0.94793457

00:57:44.070 --> 00:57:45.190 so the positive predictive value

NOTE Confidence: 0.94793457

00:57:45.190 --> 00:57:46.790 is dependent on which population

NOTE Confidence: 0.94793457

00:57:46.790 --> 00:57:47.670 you're studying in. And if

NOTE Confidence: 0.94793457

00:57:47.670 --> 00:57:48.790 you're it's a twenty year

NOTE Confidence: 0.94793457

00:57:48.790 --> 00:57:50.150 old, right, two to two

NOTE Confidence: 0.94793457

00:57:50.150 --> 00:57:51.350 to five fold high risk

NOTE Confidence: 0.94793457

00:57:51.350 --> 00:57:52.644 is just a positive predictive

NOTE Confidence: 0.94793457

00:57:52.644 --> 00:57:54.005 value of maybe two two

NOTE Confidence: 0.94793457

00:57:54.005 --> 00:57:55.204 percent. Right? Because most of

NOTE Confidence: 0.94793457

00:57:55.204 --> 00:57:56.244 those people aren't gonna get

NOTE Confidence: 0.94793457

00:57:56.244 --> 00:57:57.525 coronary disease. If you apply

NOTE Confidence: 0.94793457

00:57:57.525 --> 00:57:59.224 to a secondary prevention population

NOTE Confidence: 0.94793457

00:57:59.285 --> 00:58:00.164 in, like, the four year

NOTE Confidence: 0.94793457

00:58:00.164 --> 00:58:01.845 trial, the positive predictive value

NOTE Confidence: 0.94793457

00:58:01.845 --> 00:58:02.585 is much higher.

NOTE Confidence: 0.9498664

00:58:03.045 --> 00:58:04.885 But, yeah, the incremental that

NOTE Confidence: 0.9498664

00:58:04.885 --> 00:58:06.480 that value is small, but

NOTE Confidence: 0.9498664

00:58:06.480 --> 00:58:07.600 it it was I I

NOTE Confidence: 0.9498664

00:58:07.600 --> 00:58:08.720 think the the take home

NOTE Confidence: 0.9498664

00:58:08.720 --> 00:58:09.760 for me was that there

NOTE Confidence: 0.9498664

00:58:09.760 --> 00:58:11.119 was a treatment interaction, and

NOTE Confidence: 0.9498664

00:58:11.119 --> 00:58:12.480 that was only seen with

NOTE Confidence: 0.9498664

00:58:12.480 --> 00:58:14.260 one pathway, but not others.

NOTE Confidence: 0.99060464

00:58:14.560 --> 00:58:15.840 And so if we could

NOTE Confidence: 0.99060464

00:58:15.840 --> 00:58:17.840 refine the treatment interaction, then

NOTE Confidence: 0.99060464

00:58:17.840 --> 00:58:19.700 we could personalize treatment decisions.

NOTE Confidence: 0.99847

00:58:20.000 --> 00:58:21.280 But in just predicting who

NOTE Confidence: 0.99847

00:58:21.280 --> 00:58:22.455 gets disease or not,

NOTE Confidence: 0.9715719

00:58:23.015 --> 00:58:23.995 you know, we have better

NOTE Confidence: 0.9715719

00:58:24.135 --> 00:58:25.595 metrics for that. Age,

NOTE Confidence: 0.9173258

00:58:25.975 --> 00:58:27.435 serum cholesterol, hypertension,

NOTE Confidence: 0.99302036

00:58:27.735 --> 00:58:28.935 you know, the the Framingham

NOTE Confidence: 0.99302036

00:58:28.935 --> 00:58:29.895 risk score is, you know,

NOTE Confidence: 0.99302036

00:58:29.895 --> 00:58:30.855 much better at that than

NOTE Confidence: 0.99302036

00:58:30.855 --> 00:58:31.755 these risk scores.

NOTE Confidence: 0.83961797

00:58:32.775 --> 00:58:34.535 So, Raju, very nice talk,

NOTE Confidence: 0.83961797

00:58:34.535 --> 00:58:34.775 and,

NOTE Confidence: 0.9995465

00:58:35.390 --> 00:58:36.750 I have two questions.

NOTE Confidence: 0.9159542

00:58:37.230 --> 00:58:38.350 One is that, actually, you

NOTE Confidence: 0.9159542

00:58:38.350 --> 00:58:40.270 showed very nicely, actually, that,

NOTE Confidence: 0.9159542

00:58:40.590 --> 00:58:42.510 for example, IRX three Mhmm.

NOTE Confidence: 0.9159542

00:58:42.590 --> 00:58:43.710 Is actually a gene for

NOTE Confidence: 0.9159542

00:58:43.710 --> 00:58:45.410 obesity, while actually the variant

NOTE Confidence: 0.9159542

00:58:45.470 --> 00:58:46.670 is in the FTO gene.

NOTE Confidence: 0.9159542

00:58:46.670 --> 00:58:48.670 Right? So means that, actually,

NOTE Confidence: 0.9159542

00:58:48.670 --> 00:58:49.170 the

NOTE Confidence: 0.9215412

00:58:49.695 --> 00:58:51.475 locals doesn't mean gene itself.

NOTE Confidence: 0.8131219

00:58:51.855 --> 00:58:52.975 In a per terpsi, you

NOTE Confidence: 0.8131219

00:58:52.975 --> 00:58:54.435 actually went after the

NOTE Confidence: 0.8153117

00:58:54.735 --> 00:58:56.255 gene within the loci, not

NOTE Confidence: 0.8153117

00:58:56.255 --> 00:58:57.375 knowing that each is this

NOTE Confidence: 0.8153117

00:58:57.375 --> 00:58:59.295 variant actually regulates Sure. Or

NOTE Confidence: 0.8153117

00:58:59.295 --> 00:59:00.655 not. So I was wondering

NOTE Confidence: 0.8153117

00:59:00.655 --> 00:59:01.615 actually it would be actually

NOTE Confidence: 0.8153117

00:59:01.615 --> 00:59:02.815 based anything, maybe the next

NOTE Confidence: 0.8153117

00:59:02.815 --> 00:59:03.855 step to go rather than

NOTE Confidence: 0.8153117

00:59:03.855 --> 00:59:05.315 actually in per terpsi.

NOTE Confidence: 0.8311128

00:59:05.990 --> 00:59:07.349 And then the second question,

NOTE Confidence: 0.8311128

00:59:07.349 --> 00:59:08.470 when you're cleaning, when you're

NOTE Confidence: 0.8311128

00:59:08.470 --> 00:59:09.910 so calm, you actually always

NOTE Confidence: 0.8311128

00:59:09.910 --> 00:59:11.270 think about, you know, cascade

NOTE Confidence: 0.8311128

00:59:11.270 --> 00:59:13.050 screening, you know, etcetera.

NOTE Confidence: 0.9601838

00:59:13.510 --> 00:59:14.809 While the polygenic,

NOTE Confidence: 0.9624633

00:59:15.190 --> 00:59:16.230 you know, is gonna be

NOTE Confidence: 0.9624633

00:59:16.230 --> 00:59:17.430 distributed, it's not gonna be

NOTE Confidence: 0.9624633

00:59:17.430 --> 00:59:18.329 actually segregating

NOTE Confidence: 0.83511895

00:59:18.735 --> 00:59:20.655 perfectly. Right. And, also, often,

NOTE Confidence: 0.83511895

00:59:20.655 --> 00:59:21.775 you have actually patients to

NOTE Confidence: 0.83511895

00:59:21.775 --> 00:59:22.755 actually have families.

NOTE Confidence: 0.94788337

00:59:23.055 --> 00:59:24.575 Mhmm. So have you looked

NOTE Confidence: 0.94788337

00:59:24.575 --> 00:59:25.635 at to see actually

NOTE Confidence: 0.8481594

00:59:26.495 --> 00:59:28.255 how many how actually effective

NOTE Confidence: 0.8481594

00:59:28.255 --> 00:59:29.295 is this use use of

NOTE Confidence: 0.8481594

00:59:29.295 --> 00:59:29.615 this,

NOTE Confidence: 0.9280014

00:59:30.255 --> 00:59:31.390 kind of of yeah. Yeah.

NOTE Confidence: 0.9280014

00:59:31.390 --> 00:59:32.670 Yeah. Great. So, like, yeah.

NOTE Confidence: 0.9280014

00:59:32.670 --> 00:59:34.270 Great. Very basic question and

NOTE Confidence: 0.9280014

00:59:34.270 --> 00:59:35.710 very clinical questions. I'll try

NOTE Confidence: 0.9280014

00:59:35.710 --> 00:59:37.070 to try to switch switch

NOTE Confidence: 0.9280014

00:59:37.070 --> 00:59:38.110 gears as quickly as you

NOTE Confidence: 0.9280014

00:59:38.110 --> 00:59:39.630 can. So the first is

NOTE Confidence: 0.9280014

00:59:39.630 --> 00:59:40.770 the the the

NOTE Confidence: 0.94243574

00:59:41.310 --> 00:59:42.750 the true way that we

NOTE Confidence: 0.94243574

00:59:42.750 --> 00:59:44.904 generate the these risk of

NOTE Confidence: 0.94243574

00:59:44.904 --> 00:59:46.904 variance. Right? So, yes, we

NOTE Confidence: 0.94243574

00:59:46.904 --> 00:59:48.605 perturbacy targeted the genes.

NOTE Confidence: 0.97095996

00:59:48.984 --> 00:59:50.025 And then the way we

NOTE Confidence: 0.97095996

00:59:50.025 --> 00:59:51.145 look for enrichment, the way

NOTE Confidence: 0.97095996

00:59:51.145 --> 00:59:52.505 we found the SNPs is

NOTE Confidence: 0.97095996

00:59:52.505 --> 00:59:53.964 we we have this computational

NOTE Confidence: 0.97095996

00:59:54.025 --> 00:59:55.145 pipeline that I did not

NOTE Confidence: 0.97095996

00:59:55.145 --> 00:59:56.105 bore you with, but it's

NOTE Confidence: 0.97095996

00:59:56.105 --> 00:59:57.305 called variant to gene to

NOTE Confidence: 0.97095996

00:59:57.305 --> 00:59:57.805 program.

NOTE Confidence: 0.9624851

00:59:58.230 --> 00:59:59.510 And so we actually start

NOTE Confidence: 0.9624851

00:59:59.510 --> 01:00:00.410 with the snips,

NOTE Confidence: 0.9684929

01:00:00.790 --> 01:00:01.990 make a list of candidate

NOTE Confidence: 0.9684929

01:00:01.990 --> 01:00:02.490 genes,

NOTE Confidence: 0.9275568

01:00:02.869 --> 01:00:04.230 like, so every gene that

NOTE Confidence: 0.9275568

01:00:04.230 --> 01:00:05.270 could be regulated. And we

NOTE Confidence: 0.9275568

01:00:05.270 --> 01:00:06.090 use computational,

NOTE Confidence: 0.90097314

01:00:06.869 --> 01:00:08.550 algorithms for that, activity by

NOTE Confidence: 0.90097314

01:00:08.550 --> 01:00:09.750 contact, which was developed by

NOTE Confidence: 0.90097314

01:00:09.750 --> 01:00:11.115 Jesse Angrance's lab or,

NOTE Confidence: 0.7029667

01:00:11.675 --> 01:00:12.175 EQTLs.

NOTE Confidence: 0.974296

01:00:12.555 --> 01:00:13.275 We we have a list

NOTE Confidence: 0.974296

01:00:13.275 --> 01:00:14.795 of candidate genes. Right. And

NOTE Confidence: 0.974296

01:00:14.795 --> 01:00:15.595 then we look for the

NOTE Confidence: 0.974296

01:00:15.595 --> 01:00:17.275 pathways where those candidate genes

NOTE Confidence: 0.974296

01:00:17.275 --> 01:00:17.855 are enriched.

NOTE Confidence: 0.99688137

01:00:18.155 --> 01:00:19.455 And so we are

NOTE Confidence: 0.9341542

01:00:19.835 --> 01:00:21.035 going back to the variant,

NOTE Confidence: 0.9341542

01:00:21.035 --> 01:00:22.255 the non coding variant.

NOTE Confidence: 0.9283976

01:00:22.955 --> 01:00:24.250 And but you so so

NOTE Confidence: 0.9283976

01:00:24.250 --> 01:00:25.610 so only seventy percent of

NOTE Confidence: 0.9283976

01:00:25.610 --> 01:00:26.730 the time is our causal

NOTE Confidence: 0.9283976

01:00:26.730 --> 01:00:28.250 gene the closest gene. Right.

NOTE Confidence: 0.9283976

01:00:28.250 --> 01:00:29.450 So that so so so

NOTE Confidence: 0.9283976

01:00:29.450 --> 01:00:30.730 do account for that. Would

NOTE Confidence: 0.9283976

01:00:30.730 --> 01:00:31.850 base editing be a better

NOTE Confidence: 0.9283976

01:00:31.850 --> 01:00:33.070 way? Theoretically,

NOTE Confidence: 0.9922663

01:00:33.530 --> 01:00:34.650 but you would have to

NOTE Confidence: 0.9922663

01:00:34.650 --> 01:00:36.190 sequence a lot more cells

NOTE Confidence: 0.9922663

01:00:36.444 --> 01:00:37.805 because the effect sizes are

NOTE Confidence: 0.9922663

01:00:37.805 --> 01:00:38.924 so small. So, you know,

NOTE Confidence: 0.9922663

01:00:38.924 --> 01:00:39.885 we got away with only

NOTE Confidence: 0.9922663

01:00:39.885 --> 01:00:41.005 ninety cells per gene, and

NOTE Confidence: 0.9922663

01:00:41.005 --> 01:00:41.964 it still cost us eighty

NOTE Confidence: 0.9922663

01:00:41.964 --> 01:00:42.924 thousand dollars to do this

NOTE Confidence: 0.9922663

01:00:42.924 --> 01:00:43.424 experiment.

NOTE Confidence: 0.99543154

01:00:44.444 --> 01:00:45.484 If we were gonna do

NOTE Confidence: 0.99543154

01:00:45.484 --> 01:00:47.005 base editing, this experiment would

NOTE Confidence: 0.99543154

01:00:47.005 --> 01:00:48.704 be impossible to perform.

NOTE Confidence: 0.90143144

01:00:49.005 --> 01:00:50.829 The clinical question k. This

NOTE Confidence: 0.90143144

01:00:50.829 --> 01:00:52.109 is, like, a few shifts.

NOTE Confidence: 0.90143144

01:00:52.109 --> 01:00:53.410 So, you know, are we

NOTE Confidence: 0.98600197

01:00:53.710 --> 01:00:55.069 able to actually apply these,

NOTE Confidence: 0.98600197

01:00:55.069 --> 01:00:56.030 you know, since they don't

NOTE Confidence: 0.98600197

01:00:56.030 --> 01:00:57.230 segregate? Like, do they have

NOTE Confidence: 0.98600197

01:00:57.230 --> 01:00:58.849 any clinical predictive value?

NOTE Confidence: 0.99868244

01:00:59.630 --> 01:01:00.130 So

NOTE Confidence: 0.97017205

01:01:00.510 --> 01:01:01.630 I'm a little biased. I

NOTE Confidence: 0.97017205

01:01:01.630 --> 01:01:03.150 don't think for coronary disease,

NOTE Confidence: 0.97017205

01:01:03.150 --> 01:01:04.510 the polygenic risk score is

NOTE Confidence: 0.97017205

01:01:04.510 --> 01:01:06.210 that useful. I think this

NOTE Confidence: 0.99802697

01:01:06.725 --> 01:01:07.305 possibility that

NOTE Confidence: 0.96978563

01:01:08.085 --> 01:01:08.965 we will one day have

NOTE Confidence: 0.96978563

01:01:08.965 --> 01:01:10.325 targeted therapies or it could

NOTE Confidence: 0.96978563

01:01:10.325 --> 01:01:12.165 motivate the generation of an

NOTE Confidence: 0.96978563

01:01:12.165 --> 01:01:14.005 endothelial cell specific therapy, that's

NOTE Confidence: 0.96978563

01:01:14.005 --> 01:01:15.145 where the excitement is.

NOTE Confidence: 0.9655109

01:01:15.605 --> 01:01:17.705 But for other vascular diseases,

NOTE Confidence: 0.9655109

01:01:17.925 --> 01:01:18.805 kind of building on this

NOTE Confidence: 0.9655109

01:01:18.805 --> 01:01:20.005 framework, I do think this

NOTE Confidence: 0.9655109

01:01:20.005 --> 01:01:21.285 is actually super interesting. So

NOTE Confidence: 0.9655109

01:01:21.285 --> 01:01:21.960 I see a lot of

NOTE Confidence: 0.9655109

01:01:21.960 --> 01:01:23.420 people with thoracic aortic aneurysm,

NOTE Confidence: 0.9901707

01:01:23.960 --> 01:01:25.000 most of whom don't have

NOTE Confidence: 0.9901707

01:01:25.000 --> 01:01:26.680 a Mendelian cause, but the

NOTE Confidence: 0.9901707

01:01:26.680 --> 01:01:27.980 polygenic risk score

NOTE Confidence: 0.9793202

01:01:28.760 --> 01:01:29.960 is kind of providing that

NOTE Confidence: 0.9793202

01:01:29.960 --> 01:01:30.920 they have, like, just the

NOTE Confidence: 0.9793202

01:01:30.920 --> 01:01:32.780 polygenic risk of, like, dysfunctional

NOTE Confidence: 0.9793202

01:01:32.920 --> 01:01:35.000 and extracellular matrix. And so

NOTE Confidence: 0.9793202

01:01:35.000 --> 01:01:36.615 it gives them some sort

NOTE Confidence: 0.9793202

01:01:36.615 --> 01:01:37.494 of, you know, peace of

NOTE Confidence: 0.9793202

01:01:37.494 --> 01:01:38.775 mind that they don't have

NOTE Confidence: 0.9793202

01:01:38.775 --> 01:01:40.135 a Mendelian variant that they're

NOTE Confidence: 0.9793202

01:01:40.135 --> 01:01:41.255 passing down in their family,

NOTE Confidence: 0.9793202

01:01:41.255 --> 01:01:42.215 but they do have genetic

NOTE Confidence: 0.9793202

01:01:42.215 --> 01:01:43.595 risk as they suspect it.

NOTE Confidence: 0.9793202

01:01:43.655 --> 01:01:44.615 And so for some of

NOTE Confidence: 0.9793202

01:01:44.615 --> 01:01:45.735 those diseases, I think the

NOTE Confidence: 0.9793202

01:01:45.735 --> 01:01:46.775 benefit is more. But for

NOTE Confidence: 0.9793202

01:01:46.775 --> 01:01:47.755 coronary disease,

NOTE Confidence: 0.9970153

01:01:48.055 --> 01:01:49.015 I think our other risk

NOTE Confidence: 0.9970153

01:01:49.015 --> 01:01:50.315 scores are are adequate.

NOTE Confidence: 0.8709011

01:01:53.150 --> 01:01:53.790 We only have a few

NOTE Confidence: 0.8709011

01:01:53.790 --> 01:01:54.750 minutes. I I want,

NOTE Confidence: 0.8679147

01:01:56.190 --> 01:01:57.470 John to ask perhaps the

NOTE Confidence: 0.8679147

01:01:57.470 --> 01:01:58.670 last question. I'll have a

NOTE Confidence: 0.8679147

01:01:58.670 --> 01:01:59.950 follow-up. I can just cut

NOTE Confidence: 0.8679147

01:01:59.950 --> 01:02:00.990 to this. Go. That's fine.

NOTE Confidence: 0.8679147

01:02:00.990 --> 01:02:02.770 Sure. Mhmm. That's really good.

NOTE Confidence: 0.982327

01:02:03.070 --> 01:02:03.730 Thank you.

NOTE Confidence: 0.87805015

01:02:04.110 --> 01:02:06.050 The sequencing is in blood

NOTE Confidence: 0.87805015

01:02:06.190 --> 01:02:07.410 endothelial cells.

NOTE Confidence: 0.7058164

01:02:08.135 --> 01:02:09.835 Sorry. The perturbed sequencing?

NOTE Confidence: 0.71866024

01:02:10.615 --> 01:02:11.815 No. And for the patient,

NOTE Confidence: 0.71866024

01:02:11.815 --> 01:02:12.714 both the.

NOTE Confidence: 0.9270169

01:02:13.095 --> 01:02:14.535 Right. Yeah. All blood. Exactly.

NOTE Confidence: 0.9270169

01:02:14.535 --> 01:02:15.595 So, you know, it's

NOTE Confidence: 0.77283704

01:02:15.974 --> 01:02:16.795 true for.

NOTE Confidence: 0.9366558

01:02:17.494 --> 01:02:19.095 Yes. But how does somatic

NOTE Confidence: 0.9366558

01:02:19.335 --> 01:02:20.775 No. Right. And how does

NOTE Confidence: 0.9366558

01:02:20.775 --> 01:02:22.555 that play into your polygenic

NOTE Confidence: 0.9366558

01:02:22.694 --> 01:02:24.530 risk score? Yeah. Completely unknown.

NOTE Confidence: 0.9366558

01:02:24.670 --> 01:02:25.390 Right? So,

NOTE Confidence: 0.9641028

01:02:26.430 --> 01:02:28.030 we're really only powered to

NOTE Confidence: 0.9641028

01:02:28.030 --> 01:02:29.230 find the effects of germline

NOTE Confidence: 0.9641028

01:02:29.230 --> 01:02:30.450 mutations that are easier.

NOTE Confidence: 0.9637792

01:02:31.470 --> 01:02:32.990 But somatic variation, I think,

NOTE Confidence: 0.9637792

01:02:32.990 --> 01:02:34.430 drives disease as people have

NOTE Confidence: 0.9637792

01:02:34.430 --> 01:02:36.605 shown with CHIP. But, even

NOTE Confidence: 0.9637792

01:02:36.605 --> 01:02:37.964 like like, what you know?

NOTE Confidence: 0.9637792

01:02:37.964 --> 01:02:39.244 So CHIP is one example

NOTE Confidence: 0.9637792

01:02:39.244 --> 01:02:40.285 of somatic variation in the

NOTE Confidence: 0.9637792

01:02:40.285 --> 01:02:41.645 blood. But what about somatic

NOTE Confidence: 0.9637792

01:02:41.645 --> 01:02:42.925 variation in the blood vessel?

NOTE Confidence: 0.9637792

01:02:42.925 --> 01:02:44.045 We'll never be able to

NOTE Confidence: 0.9637792

01:02:44.045 --> 01:02:45.325 explain that. And I'll say

NOTE Confidence: 0.9637792

01:02:45.325 --> 01:02:46.365 that, you know, this pathway

NOTE Confidence: 0.9637792

01:02:46.365 --> 01:02:47.964 that I've implicated, the CCM

NOTE Confidence: 0.9637792

01:02:47.964 --> 01:02:48.464 pathway,

NOTE Confidence: 0.99934137

01:02:48.845 --> 01:02:50.145 it's very well known

NOTE Confidence: 0.9713865

01:02:50.450 --> 01:02:51.810 that the reason people form

NOTE Confidence: 0.9713865

01:02:51.810 --> 01:02:52.930 these lesions is they have

NOTE Confidence: 0.9713865

01:02:52.930 --> 01:02:54.310 one germline mutation,

NOTE Confidence: 0.9041978

01:02:54.610 --> 01:02:55.410 and then they have a

NOTE Confidence: 0.9041978

01:02:55.410 --> 01:02:57.250 second somatic variant. And maybe

NOTE Confidence: 0.9041978

01:02:57.250 --> 01:02:58.290 that's the same with coronary

NOTE Confidence: 0.9041978

01:02:58.290 --> 01:02:59.370 disease. Right? It's, you know,

NOTE Confidence: 0.9041978

01:02:59.370 --> 01:03:00.370 the the sort of a

NOTE Confidence: 0.9041978

01:03:00.370 --> 01:03:01.810 combination of the two. And

NOTE Confidence: 0.9041978

01:03:01.810 --> 01:03:03.080 so as a patient. Well

NOTE Confidence: 0.9041978

01:03:03.330 --> 01:03:04.070 Right. Exactly.

NOTE Confidence: 0.9772323

01:03:04.925 --> 01:03:06.365 Right. Right. So so, you

NOTE Confidence: 0.9772323

01:03:06.365 --> 01:03:07.645 know, maybe one day, right,

NOTE Confidence: 0.9772323

01:03:07.645 --> 01:03:08.845 you know, the the the

NOTE Confidence: 0.9772323

01:03:08.845 --> 01:03:10.625 direct sequencing for somatic variation

NOTE Confidence: 0.9772323

01:03:10.685 --> 01:03:12.525 and enough coronary plaques will

NOTE Confidence: 0.9772323

01:03:12.525 --> 01:03:13.725 answer that question, but we

NOTE Confidence: 0.9772323

01:03:13.725 --> 01:03:15.105 haven't even touched that. Right?

NOTE Confidence: 0.9763028

01:03:16.285 --> 01:03:17.640 So first of all, thank

NOTE Confidence: 0.9763028

01:03:17.640 --> 01:03:18.839 you so much for this

NOTE Confidence: 0.9763028

01:03:18.839 --> 01:03:19.880 wonderful talk. I had a

NOTE Confidence: 0.9763028

01:03:19.880 --> 01:03:21.900 very brief kinda observation question,

NOTE Confidence: 0.94609535

01:03:22.280 --> 01:03:23.660 maybe more into the application

NOTE Confidence: 0.94609535

01:03:23.880 --> 01:03:25.720 perspective. So I found,

NOTE Confidence: 0.7555791

01:03:27.079 --> 01:03:27.579 your,

NOTE Confidence: 0.8973736

01:03:28.280 --> 01:03:29.559 you sharing the data from

NOTE Confidence: 0.8973736

01:03:29.559 --> 01:03:31.579 Fourier and Jupyter really

NOTE Confidence: 0.991486

01:03:31.974 --> 01:03:33.015 quite quite interesting. I think

NOTE Confidence: 0.991486

01:03:33.015 --> 01:03:33.974 one of the challenges you've

NOTE Confidence: 0.991486

01:03:33.974 --> 01:03:35.175 identified is the importance of

NOTE Confidence: 0.991486

01:03:35.175 --> 01:03:36.795 developing new targets for

NOTE Confidence: 0.943403

01:03:37.415 --> 01:03:39.015 new new mechanisms that we

NOTE Confidence: 0.943403

01:03:39.015 --> 01:03:40.474 are even unaware. So

NOTE Confidence: 0.9559358

01:03:41.255 --> 01:03:42.214 have you tried to turn

NOTE Confidence: 0.9559358

01:03:42.214 --> 01:03:43.335 this on the on on

NOTE Confidence: 0.9559358

01:03:43.335 --> 01:03:44.454 its head a little bit?

NOTE Confidence: 0.9559358

01:03:44.454 --> 01:03:45.595 Because arguably,

NOTE Confidence: 0.8546064

01:03:46.390 --> 01:03:47.670 it would have made,

NOTE Confidence: 0.96370536

01:03:48.150 --> 01:03:50.230 Nihar's career much shorter if

NOTE Confidence: 0.96370536

01:03:50.230 --> 01:03:51.830 he hadn't enrolled eleven thousand

NOTE Confidence: 0.96370536

01:03:51.830 --> 01:03:53.050 patients. But perhaps

NOTE Confidence: 0.8820176

01:03:53.910 --> 01:03:54.730 by defining

NOTE Confidence: 0.9809247

01:03:55.350 --> 01:03:56.430 this in this, you know,

NOTE Confidence: 0.9809247

01:03:56.710 --> 01:03:58.575 this EC score, you could

NOTE Confidence: 0.9809247

01:03:58.575 --> 01:04:00.734 have identified a pathway to

NOTE Confidence: 0.9809247

01:04:00.734 --> 01:04:02.734 either fail quickly or succeed

NOTE Confidence: 0.9809247

01:04:02.734 --> 01:04:03.234 rapidly,

NOTE Confidence: 0.9642637

01:04:04.095 --> 01:04:05.535 with regards to targeting a

NOTE Confidence: 0.9642637

01:04:05.535 --> 01:04:06.815 population risk. And and I'm

NOTE Confidence: 0.9642637

01:04:06.815 --> 01:04:08.655 curious if you've been thinking

NOTE Confidence: 0.9642637

01:04:08.655 --> 01:04:10.974 about applying this even though

NOTE Confidence: 0.9642637

01:04:10.974 --> 01:04:11.875 it's not driving

NOTE Confidence: 0.9988156

01:04:12.494 --> 01:04:13.395 a new target

NOTE Confidence: 0.99846137

01:04:13.800 --> 01:04:15.980 to a mechanism of evaluating

NOTE Confidence: 0.94515187

01:04:16.280 --> 01:04:18.280 therapeutics quicker. Right. Right. Yeah.

NOTE Confidence: 0.94515187

01:04:18.280 --> 01:04:19.400 So that is actually kinda

NOTE Confidence: 0.94515187

01:04:19.400 --> 01:04:20.780 one of the exciting applications

NOTE Confidence: 0.94515187

01:04:20.840 --> 01:04:21.740 of this is that

NOTE Confidence: 0.8615482

01:04:22.120 --> 01:04:23.260 could you just enrich

NOTE Confidence: 0.96736294

01:04:23.640 --> 01:04:25.580 your your clinical trial population

NOTE Confidence: 0.96736294

01:04:25.800 --> 01:04:26.920 for people at the extreme

NOTE Confidence: 0.96736294

01:04:26.920 --> 01:04:28.005 of a polygenic risk score?

NOTE Confidence: 0.96736294

01:04:28.164 --> 01:04:29.285 Then instead of enrolling eleven

NOTE Confidence: 0.96736294

01:04:29.285 --> 01:04:30.904 thousand, you enroll four thousand,

NOTE Confidence: 0.96736294

01:04:31.125 --> 01:04:32.884 and it makes cardiovascular trials

NOTE Confidence: 0.96736294

01:04:32.884 --> 01:04:34.325 much cheaper. So, you know,

NOTE Confidence: 0.96736294

01:04:34.325 --> 01:04:35.444 maybe we would have more

NOTE Confidence: 0.96736294

01:04:35.444 --> 01:04:36.585 therapies in the space.

NOTE Confidence: 0.954225

01:04:37.204 --> 01:04:38.484 And I think one thing

NOTE Confidence: 0.954225

01:04:38.484 --> 01:04:39.525 we were excited about is

NOTE Confidence: 0.954225

01:04:39.525 --> 01:04:40.964 that, normally, for a lipid

NOTE Confidence: 0.954225

01:04:40.964 --> 01:04:42.164 lowering therapy, you would have

NOTE Confidence: 0.954225

01:04:42.164 --> 01:04:43.785 used a lipid risk score.

NOTE Confidence: 0.954225

01:04:43.980 --> 01:04:45.500 But to your system's biology

NOTE Confidence: 0.954225

01:04:45.500 --> 01:04:46.859 point that, you know, maybe

NOTE Confidence: 0.954225

01:04:46.859 --> 01:04:48.080 you have to use orthogonal

NOTE Confidence: 0.954225

01:04:48.140 --> 01:04:49.260 risk scores or for different

NOTE Confidence: 0.954225

01:04:49.260 --> 01:04:50.060 therapies, you have to use

NOTE Confidence: 0.954225

01:04:50.060 --> 01:04:51.260 different risk scores to really

NOTE Confidence: 0.954225

01:04:51.260 --> 01:04:53.660 find which one truly enriches

NOTE Confidence: 0.954225

01:04:53.660 --> 01:04:54.859 for the highest risk patient

NOTE Confidence: 0.954225

01:04:54.859 --> 01:04:55.359 population.

NOTE Confidence: 0.9212296

01:04:56.220 --> 01:04:57.580 I would argue that future

NOTE Confidence: 0.9212296

01:04:57.580 --> 01:04:59.115 lipid lowering therapy should enrich

NOTE Confidence: 0.9212296

01:04:59.115 --> 01:05:00.575 for a bad EC function

NOTE Confidence: 0.9667512

01:05:00.875 --> 01:05:02.395 and not bad LDL function.

NOTE Confidence: 0.9667512

01:05:02.395 --> 01:05:03.535 But it might be also,

NOTE Confidence: 0.95585

01:05:05.515 --> 01:05:06.875 specific to each therapy. And

NOTE Confidence: 0.95585

01:05:06.875 --> 01:05:07.994 until we really understand the

NOTE Confidence: 0.95585

01:05:07.994 --> 01:05:09.195 mechanism, I don't know if

NOTE Confidence: 0.95585

01:05:09.195 --> 01:05:10.235 I can convince a drug

NOTE Confidence: 0.95585

01:05:10.235 --> 01:05:11.435 company to put all their

NOTE Confidence: 0.95585

01:05:11.435 --> 01:05:12.635 eggs in this basket. But

NOTE Confidence: 0.95585

01:05:12.635 --> 01:05:13.830 if we knew the mechanism

NOTE Confidence: 0.95585

01:05:14.070 --> 01:05:14.870 and we, you know, we

NOTE Confidence: 0.95585

01:05:14.870 --> 01:05:15.990 could convince them that, yes,

NOTE Confidence: 0.95585

01:05:15.990 --> 01:05:17.350 this makes sense, you know,

NOTE Confidence: 0.95585

01:05:17.350 --> 01:05:18.230 I think that's where I

NOTE Confidence: 0.95585

01:05:18.230 --> 01:05:19.510 just could go. Well, I

NOTE Confidence: 0.95585

01:05:19.510 --> 01:05:20.230 I think it'd be a

NOTE Confidence: 0.95585

01:05:20.230 --> 01:05:21.830 wonderful project for a certain

NOTE Confidence: 0.95585

01:05:21.830 --> 01:05:23.610 someone to do to evaluate

NOTE Confidence: 0.95913225

01:05:24.230 --> 01:05:25.270 how much money could have

NOTE Confidence: 0.95913225

01:05:25.270 --> 01:05:26.950 been saved if that was

NOTE Confidence: 0.95913225

01:05:26.950 --> 01:05:28.515 applied. Right. And use that

NOTE Confidence: 0.95913225

01:05:28.515 --> 01:05:30.035 in, in discussions with our

NOTE Confidence: 0.95913225

01:05:30.035 --> 01:05:31.395 with our colleagues in in

NOTE Confidence: 0.95913225

01:05:31.395 --> 01:05:33.155 industry. This was wonderful. Thank

NOTE Confidence: 0.95913225

01:05:33.155 --> 01:05:34.275 you so much on on

NOTE Confidence: 0.95913225

01:05:34.275 --> 01:05:35.415 behalf of all else.

NOTE Confidence: 0.9501883

01:05:39.655 --> 01:05:40.935 As everyone's leaving, I just

NOTE Confidence: 0.9501883

01:05:40.935 --> 01:05:42.535 wanna remind everyone that tomorrow

NOTE Confidence: 0.9501883

01:05:42.535 --> 01:05:43.995 morning, we have medicine,

NOTE Confidence: 0.9504442

01:05:44.455 --> 01:05:45.975 grand rounds, and our own

NOTE Confidence: 0.9504442

01:05:45.975 --> 01:05:47.995 John Forrest, will be speaking.

NOTE Confidence: 0.9775064

01:05:48.375 --> 01:05:49.735 So do your very best

NOTE Confidence: 0.9775064

01:05:49.735 --> 01:05:51.035 to attend and