WEBVTT

NOTE duration: ”01:08:19.456”

NOTE Confidence: 0.8768266

00:01:22.775 --> 00:01:23.275 Yeah.

NOTE Confidence: 0.82082665

00:03:15.215 --> 00:03:15.715 Yeah.

NOTE Confidence: 0.9677732

00:04:19.029 --> 00:04:20.790 Good afternoon, everyone. I'm Jeremy

NOTE Confidence: 0.9677732

00:04:20.790 --> 00:04:22.230 Asens. I'm the chief of

NOTE Confidence: 0.9677732

00:04:22.230 --> 00:04:23.830 pediatric cardiology. You don't often

NOTE Confidence: 0.9677732

00:04:23.830 --> 00:04:25.044 get to see the the

NOTE Confidence: 0.9677732

00:04:25.044 --> 00:04:27.044 pediatric cardiologist up here, but,

NOTE Confidence: 0.992432

00:04:27.764 --> 00:04:29.044 I'm I'm really happy to

NOTE Confidence: 0.992432

00:04:29.044 --> 00:04:30.264 introduce Ben Landis.

NOTE Confidence: 0.9933638

00:04:31.044 --> 00:04:32.565 Ben is a new member

NOTE Confidence: 0.9933638

00:04:32.565 --> 00:04:33.525 of our section. We were

NOTE Confidence: 0.9933638

00:04:33.525 --> 00:04:34.645 lucky to recruit him this

NOTE Confidence: 0.9933638

00:04:34.645 --> 00:04:35.305 past summer,

NOTE Confidence: 0.99945486

00:04:35.925 --> 00:04:36.585 and he

NOTE Confidence: 0.9846988

00:04:36.900 --> 00:04:39.300 has expertise in aortopathy, and,

NOTE Confidence: 0.9846988

00:04:39.700 --> 00:04:40.580 we thought this would be

NOTE Confidence: 0.9846988

00:04:40.580 --> 00:04:42.020 a great way to bring

NOTE Confidence: 0.9846988

00:04:42.020 --> 00:04:42.839 folks together.

NOTE Confidence: 0.97592473

00:04:43.700 --> 00:04:45.140 So, Ben, I'm just gonna

NOTE Confidence: 0.97592473

00:04:45.140 --> 00:04:46.100 give you a little background.

NOTE Confidence: 0.97592473

00:04:46.100 --> 00:04:47.400 He did his pediatric cardiology

NOTE Confidence: 0.97592473

00:04:47.460 --> 00:04:49.460 fellowship at Cincinnati Children's, which

NOTE Confidence: 0.97592473

00:04:49.460 --> 00:04:50.339 for those of you who

NOTE Confidence: 0.97592473

00:04:50.339 --> 00:04:51.800 don't know is a really

NOTE Confidence: 0.97592473

00:04:52.015 --> 00:04:53.695 world renowned place for pediatric

NOTE Confidence: 0.97592473

00:04:53.695 --> 00:04:54.195 cardiology,

NOTE Confidence: 0.9968287

00:04:54.575 --> 00:04:56.495 cardiac surgery, and pediatric cardiac

NOTE Confidence: 0.9968287

00:04:56.495 --> 00:04:57.395 related research.

NOTE Confidence: 0.9661234

00:04:57.935 --> 00:04:58.735 While he was there in

NOTE Confidence: 0.9661234

00:04:58.735 --> 00:04:59.695 addition to his fellowship, he

NOTE Confidence: 0.9661234

00:04:59.695 --> 00:05:01.375 got a graduate, certificate in

NOTE Confidence: 0.9661234

00:05:01.375 --> 00:05:01.875 bioinformatics

NOTE Confidence: 0.9898167

00:05:02.495 --> 00:05:03.695 and did a fellowship in

NOTE Confidence: 0.9898167

00:05:03.695 --> 00:05:05.775 cardiovascular genetics as well. So

NOTE Confidence: 0.9898167

00:05:05.775 --> 00:05:06.835 he's got

NOTE Confidence: 0.9883008

00:05:07.180 --> 00:05:08.620 lots of letters and things

NOTE Confidence: 0.9883008

00:05:08.620 --> 00:05:10.379 behind his name or in

NOTE Confidence: 0.9883008

00:05:10.379 --> 00:05:11.180 front of his name, I

NOTE Confidence: 0.9883008

00:05:11.180 --> 00:05:11.680 guess.

NOTE Confidence: 0.9892901

00:05:12.379 --> 00:05:13.819 He joined the faculty at

NOTE Confidence: 0.9892901

00:05:13.819 --> 00:05:15.839 Indiana University in twenty fifteen.

NOTE Confidence: 0.99882424

00:05:16.539 --> 00:05:17.580 And while he was there,

NOTE Confidence: 0.99882424

00:05:17.580 --> 00:05:18.940 he developed a research program

NOTE Confidence: 0.99882424

00:05:18.940 --> 00:05:20.940 that focused on aortopathy and

NOTE Confidence: 0.99882424

00:05:20.940 --> 00:05:22.159 congenital heart disease.

NOTE Confidence: 0.97900724

00:05:22.474 --> 00:05:24.175 His lab identified a gene,

NOTE Confidence: 0.7461583

00:05:24.714 --> 00:05:25.694 called coq

NOTE Confidence: 0.6980533

00:05:25.995 --> 00:05:26.974 u eight b,

NOTE Confidence: 0.99909663

00:05:27.435 --> 00:05:28.395 that is now known to

NOTE Confidence: 0.99909663

00:05:28.395 --> 00:05:29.914 be a genetic modifier for

NOTE Confidence: 0.99909663

00:05:29.914 --> 00:05:30.414 aortopathy.

NOTE Confidence: 0.74999106

00:05:31.354 --> 00:05:32.254 He also

NOTE Confidence: 0.99085724

00:05:32.794 --> 00:05:34.414 established a multi institutional

NOTE Confidence: 0.9966379

00:05:34.955 --> 00:05:36.014 tissue and blood

NOTE Confidence: 0.9991652

00:05:36.460 --> 00:05:36.960 bank

NOTE Confidence: 0.97702783

00:05:37.580 --> 00:05:38.779 with tissue from,

NOTE Confidence: 0.9883991

00:05:39.339 --> 00:05:41.040 adults and children with aortopathy,

NOTE Confidence: 0.9883991

00:05:41.260 --> 00:05:42.779 and that bank now has

NOTE Confidence: 0.9883991

00:05:42.779 --> 00:05:44.240 over eleven hundred specimens.

NOTE Confidence: 0.9734192

00:05:44.620 --> 00:05:46.160 And he uses that repository

NOTE Confidence: 0.96428293

00:05:46.620 --> 00:05:49.120 to do genomic analysis and

NOTE Confidence: 0.96428293

00:05:49.260 --> 00:05:50.960 phenotype, genotype linkage

NOTE Confidence: 0.997241

00:05:51.505 --> 00:05:52.005 studies.

NOTE Confidence: 0.9576467

00:05:53.505 --> 00:05:54.705 That tissue bank is in

NOTE Confidence: 0.9576467

00:05:54.705 --> 00:05:56.385 the process of making its

NOTE Confidence: 0.9576467

00:05:56.385 --> 00:05:58.705 way from Indiana to Yale,

NOTE Confidence: 0.9576467

00:05:58.705 --> 00:06:00.085 hopefully, not in the snowstorm.

NOTE Confidence: 0.9845208

00:06:01.665 --> 00:06:03.185 He, on the clinical side,

NOTE Confidence: 0.9845208

00:06:03.185 --> 00:06:04.245 developed and led

NOTE Confidence: 0.8112511

00:06:04.740 --> 00:06:05.720 a a multidisciplinary

NOTE Confidence: 0.9659345

00:06:06.339 --> 00:06:07.639 aortopathy clinic,

NOTE Confidence: 0.9984796

00:06:08.180 --> 00:06:09.460 that saw both children and

NOTE Confidence: 0.9984796

00:06:09.460 --> 00:06:10.520 adults with aortopathy.

NOTE Confidence: 0.9965461

00:06:11.220 --> 00:06:13.060 So my hope for the

NOTE Confidence: 0.9965461

00:06:13.060 --> 00:06:14.419 future here is to develop

NOTE Confidence: 0.9965461

00:06:14.419 --> 00:06:16.120 a similar model of care

NOTE Confidence: 0.9965461

00:06:16.419 --> 00:06:17.560 where we can have

NOTE Confidence: 0.97793835

00:06:17.964 --> 00:06:20.044 cross generational care where families

NOTE Confidence: 0.97793835

00:06:20.044 --> 00:06:22.384 would come to our center,

NOTE Confidence: 0.95355296

00:06:23.485 --> 00:06:25.505 both adults and children to

NOTE Confidence: 0.95355296

00:06:25.805 --> 00:06:27.805 receive their medical care, surgical

NOTE Confidence: 0.95355296

00:06:27.805 --> 00:06:28.305 care,

NOTE Confidence: 0.9951608

00:06:28.845 --> 00:06:30.145 and all of the

NOTE Confidence: 0.9505488

00:06:31.800 --> 00:06:32.839 knee and and sort of

NOTE Confidence: 0.9505488

00:06:32.839 --> 00:06:33.800 meet all of the needs

NOTE Confidence: 0.9505488

00:06:33.800 --> 00:06:35.000 that they have as families

NOTE Confidence: 0.9505488

00:06:35.000 --> 00:06:35.660 with arotopathy.

NOTE Confidence: 0.9991654

00:06:36.120 --> 00:06:36.920 And I think that would

NOTE Confidence: 0.9991654

00:06:36.920 --> 00:06:38.839 also serve as a really

NOTE Confidence: 0.9991654

00:06:38.839 --> 00:06:41.000 fertile ground for ongoing research

NOTE Confidence: 0.9991654

00:06:41.000 --> 00:06:42.620 and innovation in this space.

NOTE Confidence: 0.9991654

00:06:42.839 --> 00:06:44.220 So with all of that,

NOTE Confidence: 0.9858921

00:06:44.680 --> 00:06:45.740 here's Ben Landis.

NOTE Confidence: 0.9628061

00:06:52.575 --> 00:06:54.175 Great. Thank you very much,

NOTE Confidence: 0.9628061

00:06:54.175 --> 00:06:55.455 Jeremy. Thank you for the

NOTE Confidence: 0.9628061

00:06:55.455 --> 00:06:56.735 opportunity to talk today.

NOTE Confidence: 0.9878695

00:06:58.095 --> 00:06:59.535 It's a great opportunity to

NOTE Confidence: 0.9878695

00:06:59.535 --> 00:07:00.975 talk to a division of

NOTE Confidence: 0.9878695

00:07:00.975 --> 00:07:02.830 cardiovascular medicine as a pediatric

NOTE Confidence: 0.9878695

00:07:02.830 --> 00:07:03.970 cardiologist and,

NOTE Confidence: 0.9773445

00:07:04.430 --> 00:07:05.970 being new to to Yale.

NOTE Confidence: 0.93495107

00:07:08.190 --> 00:07:09.389 I hope, some of what

NOTE Confidence: 0.93495107

00:07:09.389 --> 00:07:10.990 I show, and talk about

NOTE Confidence: 0.93495107

00:07:10.990 --> 00:07:11.389 today,

NOTE Confidence: 0.9113865

00:07:12.110 --> 00:07:14.289 enhances your lunch experience. So,

NOTE Confidence: 0.9760256

00:07:15.725 --> 00:07:17.565 so, just a quick disclosure

NOTE Confidence: 0.9760256

00:07:17.565 --> 00:07:18.605 there. So,

NOTE Confidence: 0.9095005

00:07:19.165 --> 00:07:21.185 drastic aortic aneurysm and dissection

NOTE Confidence: 0.9326997

00:07:21.885 --> 00:07:24.225 is an aortopathy characterized by

NOTE Confidence: 0.9326997

00:07:24.365 --> 00:07:25.264 aortic dilation,

NOTE Confidence: 0.99864763

00:07:25.805 --> 00:07:26.305 histopathology

NOTE Confidence: 0.99620354

00:07:27.245 --> 00:07:29.580 that's comprised of smooth muscle

NOTE Confidence: 0.99620354

00:07:29.580 --> 00:07:30.400 cell abnormalities,

NOTE Confidence: 0.6663229

00:07:31.740 --> 00:07:32.240 accumulation

NOTE Confidence: 0.9646087

00:07:32.540 --> 00:07:35.020 of nucoid extracellular matrix, and

NOTE Confidence: 0.9646087

00:07:35.020 --> 00:07:36.540 degradation and disarray of the

NOTE Confidence: 0.9646087

00:07:36.540 --> 00:07:37.520 elastic fibers.

NOTE Confidence: 0.9751025

00:07:38.540 --> 00:07:40.720 Thoracic aortic aneurysm is typically

NOTE Confidence: 0.9751025

00:07:41.020 --> 00:07:41.520 asymptomatic,

NOTE Confidence: 0.9448115

00:07:42.699 --> 00:07:44.545 but poses a deadly risk

NOTE Confidence: 0.9448115

00:07:44.545 --> 00:07:46.325 of a thoracic aortic dissection

NOTE Confidence: 0.9448115

00:07:46.545 --> 00:07:47.905 in which there's a separation

NOTE Confidence: 0.9448115

00:07:47.905 --> 00:07:48.965 between the insimal

NOTE Confidence: 0.9573017

00:07:49.985 --> 00:07:51.264 and medial layers of the

NOTE Confidence: 0.9573017

00:07:51.264 --> 00:07:52.565 aorta can lead to,

NOTE Confidence: 0.89389277

00:07:53.585 --> 00:07:55.044 death, major complications,

NOTE Confidence: 0.9722279

00:07:55.505 --> 00:07:57.285 and including an aortic rupture.

NOTE Confidence: 0.9967299

00:07:59.310 --> 00:08:01.470 So, looking broadly at thoracic

NOTE Confidence: 0.9967299

00:08:01.470 --> 00:08:02.370 aortic aneurysm,

NOTE Confidence: 0.9985046

00:08:02.750 --> 00:08:03.870 you can define them as

NOTE Confidence: 0.9985046

00:08:03.870 --> 00:08:04.530 a heritable,

NOTE Confidence: 0.99465346

00:08:04.990 --> 00:08:06.770 bicuspid aortic valve associated

NOTE Confidence: 0.9621152

00:08:07.230 --> 00:08:08.590 sporadic, and we do see

NOTE Confidence: 0.9621152

00:08:08.590 --> 00:08:09.950 aortic dilation in the context

NOTE Confidence: 0.9621152

00:08:09.950 --> 00:08:11.890 of complex complex heart defects

NOTE Confidence: 0.9621152

00:08:11.950 --> 00:08:12.610 as well.

NOTE Confidence: 0.9724497

00:08:14.164 --> 00:08:16.324 So, this, list of genes

NOTE Confidence: 0.9724497

00:08:16.324 --> 00:08:17.604 is is taken from a

NOTE Confidence: 0.9724497

00:08:17.604 --> 00:08:19.365 a next generation sequencing panel

NOTE Confidence: 0.9724497

00:08:19.365 --> 00:08:20.965 that we would send, typically

NOTE Confidence: 0.9724497

00:08:20.965 --> 00:08:22.485 for patients who have thoracic

NOTE Confidence: 0.9724497

00:08:22.485 --> 00:08:23.384 aortic aneurysm,

NOTE Confidence: 0.9404738

00:08:23.925 --> 00:08:25.285 consisting of thirty five genes.

NOTE Confidence: 0.9404738

00:08:25.285 --> 00:08:26.724 And it, the list of

NOTE Confidence: 0.9404738

00:08:26.724 --> 00:08:28.005 genes gives some insight into

NOTE Confidence: 0.9404738

00:08:28.005 --> 00:08:29.240 the path pathophysiology

NOTE Confidence: 0.98399186

00:08:29.699 --> 00:08:31.160 that underlies the disease.

NOTE Confidence: 0.9808629

00:08:31.780 --> 00:08:32.500 And you can see here

NOTE Confidence: 0.9808629

00:08:32.500 --> 00:08:34.179 it's, includes genes important for

NOTE Confidence: 0.9808629

00:08:34.179 --> 00:08:35.559 the extracellular matrix

NOTE Confidence: 0.8413979

00:08:35.940 --> 00:08:37.059 such as FBN one and

NOTE Confidence: 0.8413979

00:08:37.059 --> 00:08:38.520 Markman syndrome associated,

NOTE Confidence: 0.986131

00:08:39.940 --> 00:08:41.459 genes important for TGF beta

NOTE Confidence: 0.986131

00:08:41.459 --> 00:08:41.959 signaling.

NOTE Confidence: 0.8924567

00:08:42.915 --> 00:08:44.274 Many of these patients will

NOTE Confidence: 0.8924567

00:08:44.274 --> 00:08:46.115 present with a syndrome of

NOTE Confidence: 0.8924567

00:08:46.115 --> 00:08:47.334 Loewe's Dietz syndrome,

NOTE Confidence: 0.9909652

00:08:48.035 --> 00:08:49.554 genes important for smooth muscle

NOTE Confidence: 0.9909652

00:08:49.554 --> 00:08:50.054 contraction,

NOTE Confidence: 0.9272942

00:08:50.915 --> 00:08:52.434 and then a a hodgepodge

NOTE Confidence: 0.9272942

00:08:52.434 --> 00:08:53.735 of other less common,

NOTE Confidence: 0.99888074

00:08:54.274 --> 00:08:54.774 genes.

NOTE Confidence: 0.9105214

00:08:55.075 --> 00:08:57.000 There's x linked associations with

NOTE Confidence: 0.9105214

00:08:57.000 --> 00:08:58.780 a, thoracic aortic aneurysm,

NOTE Confidence: 0.9770461

00:08:59.240 --> 00:09:00.280 and then as well as

NOTE Confidence: 0.9770461

00:09:00.280 --> 00:09:01.559 well, this panel will include

NOTE Confidence: 0.9770461

00:09:01.559 --> 00:09:02.220 a couple,

NOTE Confidence: 0.99350435

00:09:02.840 --> 00:09:05.100 conditions that are, autosomal recessive.

NOTE Confidence: 0.94736063

00:09:06.440 --> 00:09:07.720 Many of these genes are

NOTE Confidence: 0.94736063

00:09:07.720 --> 00:09:10.140 associated with, extra cardiac syndromic

NOTE Confidence: 0.94736063

00:09:10.200 --> 00:09:10.520 features,

NOTE Confidence: 0.9366638

00:09:11.255 --> 00:09:12.455 but some do not, such

NOTE Confidence: 0.9366638

00:09:12.455 --> 00:09:13.735 as the smooth muscle cell

NOTE Confidence: 0.9366638

00:09:13.735 --> 00:09:15.334 contractile genes typically will present

NOTE Confidence: 0.9366638

00:09:15.334 --> 00:09:15.834 with,

NOTE Confidence: 0.93974954

00:09:16.295 --> 00:09:17.415 minimal, if any,

NOTE Confidence: 0.99919915

00:09:18.214 --> 00:09:19.434 extra cardiac features.

NOTE Confidence: 0.99941826

00:09:20.214 --> 00:09:21.415 In addition to the single

NOTE Confidence: 0.99941826

00:09:21.415 --> 00:09:22.554 gene associations,

NOTE Confidence: 0.9845883

00:09:23.520 --> 00:09:24.160 there are some,

NOTE Confidence: 0.9380932

00:09:24.880 --> 00:09:27.060 abnormalities in copy number associated

NOTE Confidence: 0.9181057

00:09:27.520 --> 00:09:29.380 with disease, including Turner syndrome,

NOTE Confidence: 0.95151573

00:09:29.840 --> 00:09:31.760 monosomy x, seven q one

NOTE Confidence: 0.95151573

00:09:31.760 --> 00:09:33.140 one point two three duplication,

NOTE Confidence: 0.95151573

00:09:33.200 --> 00:09:35.060 which involves the gene elastin,

NOTE Confidence: 0.99802077

00:09:35.520 --> 00:09:36.660 as well as this duplication.

NOTE Confidence: 0.9402831

00:09:38.255 --> 00:09:39.295 So just to kind of

NOTE Confidence: 0.9402831

00:09:39.295 --> 00:09:40.655 give a picture for the

NOTE Confidence: 0.9402831

00:09:40.815 --> 00:09:41.855 a couple of conditions we're

NOTE Confidence: 0.9402831

00:09:41.855 --> 00:09:43.475 talking about today, Marfan syndrome,

NOTE Confidence: 0.9402831

00:09:43.775 --> 00:09:45.075 in addition to the aortopathy,

NOTE Confidence: 0.9985473

00:09:45.775 --> 00:09:47.795 has associated ocular findings,

NOTE Confidence: 0.99542844

00:09:48.255 --> 00:09:50.675 skeletal findings, and cutaneous findings.

NOTE Confidence: 0.9225335

00:09:51.899 --> 00:09:52.860 Loeys Dietz syndrome,

NOTE Confidence: 0.96516955

00:09:53.259 --> 00:09:55.500 has overlapping phenotypic features with

NOTE Confidence: 0.96516955

00:09:55.500 --> 00:09:56.800 Marfan syndrome. Again,

NOTE Confidence: 0.8939271

00:09:57.500 --> 00:09:58.860 commonly associated with,

NOTE Confidence: 0.9503669

00:09:59.579 --> 00:10:01.339 changes in TGF beta genes.

NOTE Confidence: 0.9503669

00:10:01.579 --> 00:10:02.379 And some of these are

NOTE Confidence: 0.9503669

00:10:02.379 --> 00:10:02.879 skeletal.

NOTE Confidence: 0.835211

00:10:03.339 --> 00:10:03.839 Hypertilarism

NOTE Confidence: 0.9794066

00:10:04.300 --> 00:10:05.199 may be a distinctive

NOTE Confidence: 0.98147583

00:10:06.074 --> 00:10:07.934 feature compared to Marfan syndrome.

NOTE Confidence: 0.98147583

00:10:07.995 --> 00:10:09.855 Bifid uvula certainly is,

NOTE Confidence: 0.9921029

00:10:10.314 --> 00:10:11.595 in about fifty percent of

NOTE Confidence: 0.9921029

00:10:11.595 --> 00:10:12.954 patients, as well as a

NOTE Confidence: 0.9921029

00:10:12.954 --> 00:10:14.814 more extensive and and diffuse,

NOTE Confidence: 0.96567965

00:10:15.595 --> 00:10:17.615 arterial involvement that often,

NOTE Confidence: 0.99676716

00:10:18.634 --> 00:10:19.134 includes,

NOTE Confidence: 0.9927186

00:10:19.915 --> 00:10:20.975 arterial tortuosity

NOTE Confidence: 0.97931594

00:10:21.890 --> 00:10:24.309 and risk for complications of,

NOTE Confidence: 0.8619132

00:10:25.090 --> 00:10:26.690 our, the distillate or as

NOTE Confidence: 0.8619132

00:10:26.690 --> 00:10:27.170 well as,

NOTE Confidence: 0.8976292

00:10:28.370 --> 00:10:29.990 branches, arterial branches.

NOTE Confidence: 0.96750784

00:10:31.650 --> 00:10:33.670 Briefly, bicuspid aortic valve associated

NOTE Confidence: 0.96750784

00:10:33.730 --> 00:10:34.230 aortopathy,

NOTE Confidence: 0.99215454

00:10:35.505 --> 00:10:36.945 Really, we have very little

NOTE Confidence: 0.99215454

00:10:36.945 --> 00:10:38.625 understanding of the genetic basis

NOTE Confidence: 0.99215454

00:10:38.625 --> 00:10:40.625 of bicuspid aortic valve, as

NOTE Confidence: 0.99215454

00:10:40.625 --> 00:10:42.225 well as the aortopathy. There's

NOTE Confidence: 0.99215454

00:10:42.225 --> 00:10:43.845 a few single gene Mendelian

NOTE Confidence: 0.99215454

00:10:43.985 --> 00:10:45.684 causes that have been identified,

NOTE Confidence: 0.99215454

00:10:45.825 --> 00:10:46.965 but these wouldn't

NOTE Confidence: 0.93612003

00:10:47.530 --> 00:10:49.130 would not be routinely tested

NOTE Confidence: 0.93612003

00:10:49.130 --> 00:10:50.250 except for notch one in

NOTE Confidence: 0.93612003

00:10:50.250 --> 00:10:51.790 the context of a clinical

NOTE Confidence: 0.93612003

00:10:51.850 --> 00:10:53.150 evaluation for TAA.

NOTE Confidence: 0.9796979

00:10:54.650 --> 00:10:56.510 In thinking about, the importance

NOTE Confidence: 0.9796979

00:10:56.570 --> 00:10:57.790 of a genetic diagnosis,

NOTE Confidence: 0.9355834

00:10:59.565 --> 00:11:00.945 when it comes to aortic

NOTE Confidence: 0.9355834

00:11:01.005 --> 00:11:01.505 risk.

NOTE Confidence: 0.9560615

00:11:02.205 --> 00:11:03.885 The twenty twenty two guidelines

NOTE Confidence: 0.9560615

00:11:03.885 --> 00:11:04.545 from the,

NOTE Confidence: 0.9648042

00:11:06.285 --> 00:11:08.785 is a excellent review that,

NOTE Confidence: 0.95973736

00:11:09.325 --> 00:11:10.684 also a set of set

NOTE Confidence: 0.95973736

00:11:10.684 --> 00:11:11.265 of recommendations

NOTE Confidence: 0.95284057

00:11:11.645 --> 00:11:12.925 that that gave good,

NOTE Confidence: 0.98636246

00:11:13.645 --> 00:11:15.670 appreciation for the the risks

NOTE Confidence: 0.98636246

00:11:15.670 --> 00:11:18.250 associated with particular genetic abnormalities.

NOTE Confidence: 0.98636246

00:11:18.390 --> 00:11:18.890 So,

NOTE Confidence: 0.9911341

00:11:19.270 --> 00:11:21.110 that includes their guidelines for

NOTE Confidence: 0.9911341

00:11:21.110 --> 00:11:22.650 the thresholds for,

NOTE Confidence: 0.9700327

00:11:23.190 --> 00:11:25.050 performing a aortic a prophylactic

NOTE Confidence: 0.9700327

00:11:25.190 --> 00:11:26.090 aortic surgery,

NOTE Confidence: 0.99930954

00:11:26.870 --> 00:11:28.330 on the proximal aorta.

NOTE Confidence: 0.98718005

00:11:28.785 --> 00:11:29.425 And as you can see,

NOTE Confidence: 0.98718005

00:11:29.425 --> 00:11:29.925 there's,

NOTE Confidence: 0.9856024

00:11:31.345 --> 00:11:33.425 the thresholds will, be lower

NOTE Confidence: 0.9856024

00:11:33.425 --> 00:11:34.704 in patients who have Marfan

NOTE Confidence: 0.9856024

00:11:34.704 --> 00:11:35.204 syndrome,

NOTE Confidence: 0.92188317

00:11:35.824 --> 00:11:36.704 as well as those who

NOTE Confidence: 0.92188317

00:11:36.704 --> 00:11:38.065 have high risk features, even

NOTE Confidence: 0.92188317

00:11:38.065 --> 00:11:40.545 lower. Lowy's Dietz syndrome, because

NOTE Confidence: 0.92188317

00:11:40.545 --> 00:11:40.785 of the,

NOTE Confidence: 0.974849

00:11:41.570 --> 00:11:43.890 data would suggest that many

NOTE Confidence: 0.974849

00:11:43.890 --> 00:11:45.090 patients have a higher risk,

NOTE Confidence: 0.974849

00:11:45.090 --> 00:11:46.690 and therefore, the thresholds are

NOTE Confidence: 0.974849

00:11:46.690 --> 00:11:48.770 lower in, the majority of

NOTE Confidence: 0.974849

00:11:48.770 --> 00:11:50.130 genes associated with Lowy's Dietz

NOTE Confidence: 0.974849

00:11:50.130 --> 00:11:51.650 syndrome. And then smooth muscle

NOTE Confidence: 0.974849

00:11:51.650 --> 00:11:53.490 contractile genes also will have

NOTE Confidence: 0.974849

00:11:53.490 --> 00:11:54.390 a lower threshold.

NOTE Confidence: 0.99872684

00:11:55.025 --> 00:11:56.325 And when there's a heritable

NOTE Confidence: 0.95044565

00:11:56.785 --> 00:11:58.545 association in the family, but

NOTE Confidence: 0.95044565

00:11:58.545 --> 00:12:00.085 a genetic cause isn't identified,

NOTE Confidence: 0.95044565

00:12:00.145 --> 00:12:00.885 there's also,

NOTE Confidence: 0.9962658

00:12:01.345 --> 00:12:02.945 consideration for surgery at a

NOTE Confidence: 0.9962658

00:12:02.945 --> 00:12:03.684 lower threshold.

NOTE Confidence: 0.9774933

00:12:04.785 --> 00:12:06.085 You know, as as mentioned,

NOTE Confidence: 0.9774933

00:12:06.385 --> 00:12:08.465 the the guidelines are extensive

NOTE Confidence: 0.9774933

00:12:08.465 --> 00:12:09.585 here, and, the high risk

NOTE Confidence: 0.9774933

00:12:09.585 --> 00:12:11.210 features generally will include things

NOTE Confidence: 0.9774933

00:12:11.210 --> 00:12:13.210 like rapid aortic dilation, family

NOTE Confidence: 0.9774933

00:12:13.210 --> 00:12:14.190 history of dissection,

NOTE Confidence: 0.9366493

00:12:15.050 --> 00:12:16.890 morph morphology of the proximal

NOTE Confidence: 0.9366493

00:12:16.890 --> 00:12:18.250 aorta, whether it's root and

NOTE Confidence: 0.9366493

00:12:18.250 --> 00:12:18.750 ascending,

NOTE Confidence: 0.9380791

00:12:19.370 --> 00:12:20.589 involvement, for example,

NOTE Confidence: 0.99039125

00:12:20.890 --> 00:12:22.429 if there's arterial tortuosity,

NOTE Confidence: 0.9676731

00:12:23.210 --> 00:12:24.170 as well as some some,

NOTE Confidence: 0.9643359

00:12:24.774 --> 00:12:26.615 attention to non cardiovascular abnormalities

NOTE Confidence: 0.9643359

00:12:26.615 --> 00:12:27.654 in the context of Loeys

NOTE Confidence: 0.9643359

00:12:27.654 --> 00:12:29.895 Dietz syndrome, potentially indicating more

NOTE Confidence: 0.9643359

00:12:29.895 --> 00:12:30.795 severe phenotype.

NOTE Confidence: 0.9794664

00:12:33.015 --> 00:12:33.815 So I was gonna go

NOTE Confidence: 0.9794664

00:12:33.815 --> 00:12:35.975 through, some recent studies that

NOTE Confidence: 0.9794664

00:12:35.975 --> 00:12:36.475 highlight,

NOTE Confidence: 0.9990461

00:12:37.015 --> 00:12:37.755 some associations

NOTE Confidence: 0.99398655

00:12:38.295 --> 00:12:40.315 between genes and risk.

NOTE Confidence: 0.99137765

00:12:40.860 --> 00:12:41.740 And so on the left

NOTE Confidence: 0.99137765

00:12:41.740 --> 00:12:42.240 here,

NOTE Confidence: 0.9873564

00:12:43.020 --> 00:12:44.800 is is a a plot

NOTE Confidence: 0.9873564

00:12:44.860 --> 00:12:46.460 that's, from the from a

NOTE Confidence: 0.9873564

00:12:46.460 --> 00:12:46.960 university,

NOTE Confidence: 0.93614584

00:12:47.660 --> 00:12:49.020 in Osaka in which they

NOTE Confidence: 0.93614584

00:12:49.020 --> 00:12:50.300 looked at five hundred eighteen

NOTE Confidence: 0.93614584

00:12:50.300 --> 00:12:52.220 patients. And the these studies

NOTE Confidence: 0.93614584

00:12:52.220 --> 00:12:53.900 have group genes based on

NOTE Confidence: 0.93614584

00:12:53.900 --> 00:12:55.524 on classes, essentially, especially when

NOTE Confidence: 0.93614584

00:12:55.524 --> 00:12:56.565 it comes to Loewe's Dietz

NOTE Confidence: 0.93614584

00:12:56.565 --> 00:12:57.065 syndrome.

NOTE Confidence: 0.99473566

00:12:57.445 --> 00:12:58.404 And I think what what

NOTE Confidence: 0.99473566

00:12:58.404 --> 00:12:59.684 we can appreciate here is

NOTE Confidence: 0.99473566

00:12:59.684 --> 00:13:01.285 that in patients who have,

NOTE Confidence: 0.99922496

00:13:02.485 --> 00:13:03.625 changes in genes

NOTE Confidence: 0.9858612

00:13:04.404 --> 00:13:05.684 that are involving the TGF

NOTE Confidence: 0.9858612

00:13:05.684 --> 00:13:06.825 beta signaling pathway

NOTE Confidence: 0.9912923

00:13:07.205 --> 00:13:08.565 or in the smooth muscle

NOTE Confidence: 0.9912923

00:13:08.565 --> 00:13:09.065 contractile

NOTE Confidence: 0.94770724

00:13:09.679 --> 00:13:10.880 tended to have a higher,

NOTE Confidence: 0.94770724

00:13:11.120 --> 00:13:13.120 an earlier onset of aortic

NOTE Confidence: 0.94770724

00:13:13.120 --> 00:13:14.800 events, including dissections need for

NOTE Confidence: 0.94770724

00:13:14.800 --> 00:13:15.699 aortic surgery.

NOTE Confidence: 0.9115259

00:13:18.079 --> 00:13:19.839 Kind of corroborating that data

NOTE Confidence: 0.9115259

00:13:19.839 --> 00:13:21.300 would be a larger study,

NOTE Confidence: 0.9115259

00:13:21.440 --> 00:13:22.975 international study, the month from

NOTE Confidence: 0.9115259

00:13:22.975 --> 00:13:24.835 the Montalcino aortic consortium

NOTE Confidence: 0.94456065

00:13:25.295 --> 00:13:26.495 in which they've looked at,

NOTE Confidence: 0.94456065

00:13:26.815 --> 00:13:28.434 patients who have vascular EDS,

NOTE Confidence: 0.87694824

00:13:29.695 --> 00:13:31.554 patients with TGF beta signaling,

NOTE Confidence: 0.87694824

00:13:31.855 --> 00:13:32.915 gene abnormalities,

NOTE Confidence: 0.97726035

00:13:33.215 --> 00:13:34.815 and Marfan syndrome. And you

NOTE Confidence: 0.97726035

00:13:34.815 --> 00:13:35.775 can pay attention. They looked

NOTE Confidence: 0.97726035

00:13:35.775 --> 00:13:37.295 at arterial complications as well

NOTE Confidence: 0.97726035

00:13:37.295 --> 00:13:37.875 as aortic

NOTE Confidence: 0.9467415

00:13:38.559 --> 00:13:39.600 complications. So you can pay

NOTE Confidence: 0.9467415

00:13:39.600 --> 00:13:41.040 attention to the dash lines

NOTE Confidence: 0.9467415

00:13:41.040 --> 00:13:42.160 here with the aortic. And

NOTE Confidence: 0.9467415

00:13:42.160 --> 00:13:43.600 again, what we're what we

NOTE Confidence: 0.9467415

00:13:43.600 --> 00:13:44.980 can appreciate here,

NOTE Confidence: 0.8923514

00:13:45.520 --> 00:13:46.800 that, you know, we started

NOTE Confidence: 0.8923514

00:13:46.800 --> 00:13:47.840 to appreciate here as well

NOTE Confidence: 0.8923514

00:13:47.840 --> 00:13:49.460 is at some point, really,

NOTE Confidence: 0.8923514

00:13:49.760 --> 00:13:50.900 the risk for

NOTE Confidence: 0.90308523

00:13:51.280 --> 00:13:51.940 a dissection

NOTE Confidence: 0.99183846

00:13:52.480 --> 00:13:53.780 starts to become fairly

NOTE Confidence: 0.9401368

00:13:54.195 --> 00:13:56.195 similar between Marfan syndrome and

NOTE Confidence: 0.9401368

00:13:56.195 --> 00:13:57.795 Loeys Dietz syndrome despite there

NOTE Confidence: 0.9401368

00:13:57.795 --> 00:13:59.255 being potentially an earlier,

NOTE Confidence: 0.99574757

00:13:59.795 --> 00:14:00.295 risk.

NOTE Confidence: 0.98002505

00:14:00.995 --> 00:14:01.655 And so,

NOTE Confidence: 0.9616249

00:14:02.195 --> 00:14:03.155 you know, I think that

NOTE Confidence: 0.9616249

00:14:03.155 --> 00:14:04.115 also we can look at

NOTE Confidence: 0.9616249

00:14:04.115 --> 00:14:05.795 these things, these risks, and

NOTE Confidence: 0.9616249

00:14:05.795 --> 00:14:07.000 it's been looked at likewise

NOTE Confidence: 0.9616249

00:14:07.000 --> 00:14:07.860 with the Montalcino,

NOTE Confidence: 0.9788289

00:14:08.399 --> 00:14:10.240 aortic consortium by looking at

NOTE Confidence: 0.9788289

00:14:10.240 --> 00:14:11.759 specific genes. And here we're

NOTE Confidence: 0.9788289

00:14:11.759 --> 00:14:13.839 seeing aortic events occurring in

NOTE Confidence: 0.9788289

00:14:13.839 --> 00:14:14.420 a similar,

NOTE Confidence: 0.98464155

00:14:14.800 --> 00:14:16.800 age dependency between smooth muscle

NOTE Confidence: 0.98464155

00:14:16.800 --> 00:14:18.559 contractile genes and TGF beta

NOTE Confidence: 0.98464155

00:14:18.559 --> 00:14:19.774 genes. Then when you look

NOTE Confidence: 0.98464155

00:14:19.774 --> 00:14:21.454 at the the specific genes

NOTE Confidence: 0.98464155

00:14:21.454 --> 00:14:22.815 within the TGF beta signaling

NOTE Confidence: 0.98464155

00:14:22.815 --> 00:14:24.495 pathway, what's starting to emerge

NOTE Confidence: 0.98464155

00:14:24.495 --> 00:14:26.015 is, patients who have mutations

NOTE Confidence: 0.98464155

00:14:26.015 --> 00:14:27.695 in TGF beta receptor one

NOTE Confidence: 0.98464155

00:14:27.695 --> 00:14:29.535 or TGF beta receptor two

NOTE Confidence: 0.98464155

00:14:29.535 --> 00:14:31.075 tend to have earlier complications,

NOTE Confidence: 0.98464155

00:14:31.375 --> 00:14:33.135 aortic events, than those with

NOTE Confidence: 0.98464155

00:14:33.135 --> 00:14:34.115 the other genes.

NOTE Confidence: 0.9758555

00:14:35.990 --> 00:14:37.350 Likewise, with smooth muscle cell

NOTE Confidence: 0.9758555

00:14:37.350 --> 00:14:37.850 genes,

NOTE Confidence: 0.8813232

00:14:38.390 --> 00:14:40.090 ACTA two seems to be,

NOTE Confidence: 0.89731634

00:14:40.550 --> 00:14:42.630 sorry, PRKG one seems to

NOTE Confidence: 0.89731634

00:14:42.630 --> 00:14:43.450 be particularly,

NOTE Confidence: 0.9690601

00:14:44.390 --> 00:14:45.770 prone to an early complication,

NOTE Confidence: 0.9813037

00:14:46.630 --> 00:14:48.230 and then followed by ACTA

NOTE Confidence: 0.9813037

00:14:48.230 --> 00:14:49.935 two changes and then MYLK,

NOTE Confidence: 0.9349232

00:14:51.035 --> 00:14:52.555 myosin like chain kinase. So

NOTE Confidence: 0.9349232

00:14:52.555 --> 00:14:53.995 these are giving some level

NOTE Confidence: 0.9349232

00:14:53.995 --> 00:14:54.394 of,

NOTE Confidence: 0.9322362

00:14:55.194 --> 00:14:56.315 insights into how we could

NOTE Confidence: 0.9322362

00:14:56.315 --> 00:14:57.995 stratify a patient's risk based

NOTE Confidence: 0.9322362

00:14:57.995 --> 00:14:58.815 on genes.

NOTE Confidence: 0.8620127

00:15:00.235 --> 00:15:00.735 So,

NOTE Confidence: 0.988771

00:15:01.200 --> 00:15:02.260 you know, with the rationale

NOTE Confidence: 0.988771

00:15:02.480 --> 00:15:04.160 there, as well as other,

NOTE Confidence: 0.988771

00:15:04.560 --> 00:15:06.080 pieces of rationale for genetic

NOTE Confidence: 0.988771

00:15:06.080 --> 00:15:07.600 testing, of course, I took

NOTE Confidence: 0.988771

00:15:07.600 --> 00:15:08.640 a look at the literature

NOTE Confidence: 0.988771

00:15:08.640 --> 00:15:09.520 in terms of what's the

NOTE Confidence: 0.988771

00:15:09.520 --> 00:15:10.800 yield when patients are coming

NOTE Confidence: 0.988771

00:15:10.800 --> 00:15:12.160 in for testing with the

NOTE Confidence: 0.988771

00:15:12.160 --> 00:15:13.755 next generation sequencing panel.

NOTE Confidence: 0.9283767

00:15:14.235 --> 00:15:15.435 And, you know, I think

NOTE Confidence: 0.9283767

00:15:15.435 --> 00:15:16.395 that over the course of

NOTE Confidence: 0.9283767

00:15:16.395 --> 00:15:18.395 time, there's different selection criteria

NOTE Confidence: 0.9283767

00:15:18.395 --> 00:15:19.435 in these studies and they're

NOTE Confidence: 0.9283767

00:15:19.435 --> 00:15:19.935 retrospective.

NOTE Confidence: 0.8925675

00:15:20.795 --> 00:15:21.375 But overall,

NOTE Confidence: 0.9688529

00:15:21.915 --> 00:15:23.435 you can see that the

NOTE Confidence: 0.9688529

00:15:23.435 --> 00:15:25.195 the likelihood of identifying a

NOTE Confidence: 0.9688529

00:15:25.195 --> 00:15:27.320 pathogenic likely pathogenic variant in

NOTE Confidence: 0.9688529

00:15:27.320 --> 00:15:28.520 in in these genes, you

NOTE Confidence: 0.9688529

00:15:28.520 --> 00:15:29.640 know, ranging from twenty to

NOTE Confidence: 0.9688529

00:15:29.640 --> 00:15:30.760 thirty six genes depending on

NOTE Confidence: 0.9688529

00:15:30.760 --> 00:15:31.340 the panel,

NOTE Confidence: 0.9736019

00:15:31.720 --> 00:15:32.760 could be four percent, but

NOTE Confidence: 0.9736019

00:15:32.760 --> 00:15:34.140 upward of eighteen percent.

NOTE Confidence: 0.99382097

00:15:34.920 --> 00:15:35.880 And I wanted to highlight

NOTE Confidence: 0.99382097

00:15:35.880 --> 00:15:37.420 here too that there's commonly

NOTE Confidence: 0.7202382

00:15:38.280 --> 00:15:39.415 variants of uncertain

NOTE Confidence: 0.9569095

00:15:39.795 --> 00:15:41.235 significance identified. And that's a

NOTE Confidence: 0.9569095

00:15:41.235 --> 00:15:42.595 real challenge when it comes

NOTE Confidence: 0.9569095

00:15:42.595 --> 00:15:43.335 to the management,

NOTE Confidence: 0.9772542

00:15:43.715 --> 00:15:45.575 and something that, you know,

NOTE Confidence: 0.9772542

00:15:45.795 --> 00:15:47.395 warrants further studies in terms

NOTE Confidence: 0.9772542

00:15:47.395 --> 00:15:49.795 of, developing novel ways to

NOTE Confidence: 0.9772542

00:15:49.795 --> 00:15:52.215 functionally interpret variants, for example.

NOTE Confidence: 0.9919435

00:15:52.760 --> 00:15:53.880 And this further shows so

NOTE Confidence: 0.9919435

00:15:53.880 --> 00:15:54.860 this is from the,

NOTE Confidence: 0.9770426

00:15:55.240 --> 00:15:56.839 an aorta clinic in in

NOTE Confidence: 0.9770426

00:15:56.839 --> 00:15:57.960 Canada, and they looked at

NOTE Confidence: 0.9770426

00:15:57.960 --> 00:15:59.080 two hundred fifty patients. And

NOTE Confidence: 0.9770426

00:15:59.080 --> 00:16:00.200 you can see that the

NOTE Confidence: 0.9770426

00:16:00.200 --> 00:16:01.740 variants of uncertain significance,

NOTE Confidence: 0.96639967

00:16:02.520 --> 00:16:04.040 which you typically wouldn't be

NOTE Confidence: 0.96639967

00:16:04.040 --> 00:16:05.880 clinically actionable, but you have

NOTE Confidence: 0.96639967

00:16:05.880 --> 00:16:07.720 to, consider some of them

NOTE Confidence: 0.96639967

00:16:07.720 --> 00:16:09.785 as potentially disease contributing.

NOTE Confidence: 0.90624154

00:16:10.565 --> 00:16:11.605 You can see that some

NOTE Confidence: 0.90624154

00:16:11.605 --> 00:16:12.485 of these are in genes

NOTE Confidence: 0.90624154

00:16:12.485 --> 00:16:13.845 that are have high significant

NOTE Confidence: 0.90624154

00:16:13.845 --> 00:16:15.625 importance at least, FBM one,

NOTE Confidence: 0.93699265

00:16:16.245 --> 00:16:18.085 you know, TGF beta two,

NOTE Confidence: 0.93699265

00:16:18.085 --> 00:16:19.685 TGF beta r one. So,

NOTE Confidence: 0.93699265

00:16:19.685 --> 00:16:20.485 you know, there's a real

NOTE Confidence: 0.93699265

00:16:20.485 --> 00:16:22.585 need for triaging or classification

NOTE Confidence: 0.93699265

00:16:22.805 --> 00:16:24.300 of variants of uncertain significance.

NOTE Confidence: 0.9664909

00:16:25.800 --> 00:16:27.800 The genetic complexity of of

NOTE Confidence: 0.9664909

00:16:27.800 --> 00:16:29.640 aortopathy also is highlighted by

NOTE Confidence: 0.9664909

00:16:29.640 --> 00:16:30.540 Marfan syndrome,

NOTE Confidence: 0.9733723

00:16:31.000 --> 00:16:32.700 so high locus heterogeneity,

NOTE Confidence: 0.9872553

00:16:33.560 --> 00:16:35.020 in this condition. So,

NOTE Confidence: 0.895654

00:16:35.400 --> 00:16:36.975 this is data I extracted

NOTE Confidence: 0.895654

00:16:36.975 --> 00:16:37.795 from ClinVar,

NOTE Confidence: 0.9603327

00:16:38.735 --> 00:16:40.175 this month. And what we're

NOTE Confidence: 0.9603327

00:16:40.175 --> 00:16:41.295 highlighting here is these are

NOTE Confidence: 0.9603327

00:16:41.295 --> 00:16:41.795 all

NOTE Confidence: 0.9696029

00:16:42.175 --> 00:16:43.695 variants that were reported in

NOTE Confidence: 0.9696029

00:16:43.695 --> 00:16:46.115 the ClinVar database, including pathogenic,

NOTE Confidence: 0.9696029

00:16:46.175 --> 00:16:47.775 likely pathogenic. And so when

NOTE Confidence: 0.9696029

00:16:47.775 --> 00:16:48.735 we look at these likely

NOTE Confidence: 0.9696029

00:16:48.735 --> 00:16:50.335 pathogenic, pathogenic variants, you can

NOTE Confidence: 0.9696029

00:16:50.335 --> 00:16:50.820 see that

NOTE Confidence: 0.9677083

00:16:51.700 --> 00:16:53.220 three thousand six hundred fifteen

NOTE Confidence: 0.9677083

00:16:53.220 --> 00:16:54.980 different variants have been associated

NOTE Confidence: 0.9677083

00:16:54.980 --> 00:16:56.740 with Marfan syndrome in FBN

NOTE Confidence: 0.9677083

00:16:56.740 --> 00:16:57.860 one. And there's a range

NOTE Confidence: 0.9677083

00:16:57.860 --> 00:16:59.460 of types of mutation there

NOTE Confidence: 0.9677083

00:16:59.460 --> 00:17:00.500 when it comes to deletion

NOTE Confidence: 0.9677083

00:17:00.500 --> 00:17:01.000 duplications

NOTE Confidence: 0.9563949

00:17:01.460 --> 00:17:02.580 as well as frame shift,

NOTE Confidence: 0.9563949

00:17:02.580 --> 00:17:04.900 missense changes, nonsense, and splice

NOTE Confidence: 0.9563949

00:17:04.900 --> 00:17:05.400 sites.

NOTE Confidence: 0.9899856

00:17:06.965 --> 00:17:07.465 Likewise,

NOTE Confidence: 0.99313176

00:17:07.925 --> 00:17:09.545 we see in the databases

NOTE Confidence: 0.92482406

00:17:09.845 --> 00:17:11.305 lots of variance of uncertain

NOTE Confidence: 0.92482406

00:17:11.365 --> 00:17:13.125 significance in FBN one. FBN

NOTE Confidence: 0.92482406

00:17:13.125 --> 00:17:14.325 one sixty five exon, so

NOTE Confidence: 0.92482406

00:17:14.325 --> 00:17:15.225 a large gene.

NOTE Confidence: 0.93832034

00:17:15.685 --> 00:17:16.965 But even in a condition

NOTE Confidence: 0.93832034

00:17:16.965 --> 00:17:18.485 like Marfan syndrome where there's

NOTE Confidence: 0.93832034

00:17:18.485 --> 00:17:19.845 lots of experience, there's still

NOTE Confidence: 0.93832034

00:17:19.845 --> 00:17:21.179 tons of uncertainty when it

NOTE Confidence: 0.93832034

00:17:21.179 --> 00:17:22.480 comes to variant interpretation,

NOTE Confidence: 0.9797495

00:17:23.980 --> 00:17:25.500 and its contribution to to

NOTE Confidence: 0.9797495

00:17:25.500 --> 00:17:26.000 disease.

NOTE Confidence: 0.77263355

00:17:27.580 --> 00:17:28.320 So the

NOTE Confidence: 0.9991403

00:17:28.700 --> 00:17:29.899 going a little bit deeper

NOTE Confidence: 0.9991403

00:17:29.899 --> 00:17:31.740 into trying to understand genetic

NOTE Confidence: 0.9991403

00:17:31.740 --> 00:17:32.240 classification

NOTE Confidence: 0.9507813

00:17:32.619 --> 00:17:33.260 and risk,

NOTE Confidence: 0.9553067

00:17:33.659 --> 00:17:35.100 this study looked at the,

NOTE Confidence: 0.98131746

00:17:35.500 --> 00:17:36.000 cumulative

NOTE Confidence: 0.96024585

00:17:36.335 --> 00:17:37.455 risk when it came to

NOTE Confidence: 0.96024585

00:17:37.455 --> 00:17:38.975 the types of FBN one

NOTE Confidence: 0.96024585

00:17:38.975 --> 00:17:40.095 variants in in patients who

NOTE Confidence: 0.96024585

00:17:40.095 --> 00:17:41.155 have Marfan syndrome.

NOTE Confidence: 0.9838902

00:17:41.535 --> 00:17:43.135 So, the thinking is that,

NOTE Confidence: 0.9838902

00:17:43.535 --> 00:17:45.295 changes in FBN one, can

NOTE Confidence: 0.9838902

00:17:45.295 --> 00:17:46.994 have a dominant negative effect,

NOTE Confidence: 0.9850794

00:17:47.455 --> 00:17:48.515 or be a haploinsufficiency

NOTE Confidence: 0.92410445

00:17:49.215 --> 00:17:50.780 mechanism. And then these these

NOTE Confidence: 0.92410445

00:17:50.780 --> 00:17:52.059 people as well identified a

NOTE Confidence: 0.92410445

00:17:52.059 --> 00:17:52.880 certain regions,

NOTE Confidence: 0.9672945

00:17:53.260 --> 00:17:54.700 in the gene where cysteine

NOTE Confidence: 0.9672945

00:17:54.700 --> 00:17:56.220 residues could be affected and

NOTE Confidence: 0.9672945

00:17:56.220 --> 00:17:57.440 may have had a more

NOTE Confidence: 0.9672945

00:17:57.500 --> 00:17:59.420 severe phenotype. And I think

NOTE Confidence: 0.9672945

00:17:59.420 --> 00:18:01.179 this data corresponds with other

NOTE Confidence: 0.9672945

00:18:01.179 --> 00:18:02.540 studies as well in which,

NOTE Confidence: 0.9672945

00:18:02.540 --> 00:18:03.980 in general, patients who have

NOTE Confidence: 0.9672945

00:18:03.980 --> 00:18:05.765 a mutation leading to haploinsufficiency

NOTE Confidence: 0.99727386

00:18:06.305 --> 00:18:07.825 have a higher risk for

NOTE Confidence: 0.99727386

00:18:07.825 --> 00:18:08.485 a complication

NOTE Confidence: 0.997049

00:18:08.865 --> 00:18:10.325 compared to those who have,

NOTE Confidence: 0.9616531

00:18:11.345 --> 00:18:13.025 what's presumed to be a

NOTE Confidence: 0.9616531

00:18:13.025 --> 00:18:14.625 dominant negative effect based on

NOTE Confidence: 0.9616531

00:18:14.625 --> 00:18:15.744 it being, for instance, a

NOTE Confidence: 0.9616531

00:18:15.744 --> 00:18:16.725 missense change.

NOTE Confidence: 0.9447281

00:18:18.619 --> 00:18:20.220 Likewise, we've started to be

NOTE Confidence: 0.9447281

00:18:20.220 --> 00:18:21.580 able to stratify bay in

NOTE Confidence: 0.9447281

00:18:21.580 --> 00:18:23.020 other genes based on variant

NOTE Confidence: 0.9447281

00:18:23.020 --> 00:18:24.960 type. And so, in TGFBR

NOTE Confidence: 0.9339208

00:18:25.260 --> 00:18:26.380 two patients, you can see

NOTE Confidence: 0.9339208

00:18:26.380 --> 00:18:28.220 that, an arginine five twenty

NOTE Confidence: 0.9339208

00:18:28.220 --> 00:18:29.260 eight had a really high

NOTE Confidence: 0.9339208

00:18:29.260 --> 00:18:30.320 risk in the Montechino

NOTE Confidence: 0.79552597

00:18:32.385 --> 00:18:33.605 for early complications.

NOTE Confidence: 0.94071233

00:18:33.985 --> 00:18:35.585 Whereas, SMAD three, when you

NOTE Confidence: 0.94071233

00:18:35.585 --> 00:18:36.625 look at the different types

NOTE Confidence: 0.94071233

00:18:36.625 --> 00:18:38.065 of changes that were reported

NOTE Confidence: 0.94071233

00:18:38.065 --> 00:18:39.665 in that data set, we

NOTE Confidence: 0.94071233

00:18:39.665 --> 00:18:40.705 really don't see a clear

NOTE Confidence: 0.94071233

00:18:40.705 --> 00:18:41.205 stratification,

NOTE Confidence: 0.9964811

00:18:42.065 --> 00:18:42.965 with risk.

NOTE Confidence: 0.9980502

00:18:43.679 --> 00:18:44.639 When it came to smooth

NOTE Confidence: 0.9980502

00:18:44.639 --> 00:18:45.940 muscle contraction genes,

NOTE Confidence: 0.96985245

00:18:46.720 --> 00:18:49.279 this, variant, affecting residue one

NOTE Confidence: 0.96985245

00:18:49.279 --> 00:18:50.179 seventy nine,

NOTE Confidence: 0.9622567

00:18:50.559 --> 00:18:51.600 in ACTA two seems to

NOTE Confidence: 0.9622567

00:18:51.600 --> 00:18:52.419 be particularly

NOTE Confidence: 0.91604155

00:18:52.720 --> 00:18:54.019 predisposing to complications.

NOTE Confidence: 0.9896035

00:18:54.960 --> 00:18:56.095 And and you can also

NOTE Confidence: 0.9896035

00:18:56.095 --> 00:18:57.615 start to identify others that

NOTE Confidence: 0.9896035

00:18:57.615 --> 00:18:59.294 that may also confer an

NOTE Confidence: 0.9896035

00:18:59.294 --> 00:19:00.274 increased risk.

NOTE Confidence: 0.9427194

00:19:00.815 --> 00:19:02.095 And then, they also looked

NOTE Confidence: 0.9427194

00:19:02.095 --> 00:19:03.455 at myosin light chain kinase

NOTE Confidence: 0.9427194

00:19:03.455 --> 00:19:05.455 variants, and and interestingly, missense

NOTE Confidence: 0.9427194

00:19:05.455 --> 00:19:06.755 variants tended to be,

NOTE Confidence: 0.8930197

00:19:07.375 --> 00:19:08.575 a a higher risk than

NOTE Confidence: 0.8930197

00:19:08.575 --> 00:19:10.260 those that were predicted to

NOTE Confidence: 0.8930197

00:19:10.260 --> 00:19:12.060 be protein truncated leading to

NOTE Confidence: 0.8930197

00:19:12.060 --> 00:19:13.600 nonsense media decay.

NOTE Confidence: 0.998845

00:19:14.140 --> 00:19:15.340 So there are efforts out

NOTE Confidence: 0.998845

00:19:15.340 --> 00:19:16.720 there to try to stratify

NOTE Confidence: 0.9178712

00:19:17.340 --> 00:19:18.780 risk based on gene, gene

NOTE Confidence: 0.9178712

00:19:18.780 --> 00:19:19.920 class, and variants.

NOTE Confidence: 0.93913156

00:19:20.460 --> 00:19:21.260 I I just wanted to

NOTE Confidence: 0.93913156

00:19:21.260 --> 00:19:22.540 highlight though that, you know,

NOTE Confidence: 0.93913156

00:19:22.540 --> 00:19:23.340 as you can see, people

NOTE Confidence: 0.93913156

00:19:23.340 --> 00:19:24.460 who are living to age

NOTE Confidence: 0.93913156

00:19:24.460 --> 00:19:25.675 fifty, for for instance, that

NOTE Confidence: 0.93913156

00:19:25.675 --> 00:19:26.575 have a,

NOTE Confidence: 0.9607169

00:19:27.275 --> 00:19:29.515 dominant negative predicted dominant negative

NOTE Confidence: 0.9607169

00:19:29.515 --> 00:19:31.035 variant. You can see it's

NOTE Confidence: 0.9607169

00:19:31.035 --> 00:19:32.955 not it's around fifty percent

NOTE Confidence: 0.9607169

00:19:32.955 --> 00:19:34.734 of individuals are having complications.

NOTE Confidence: 0.9607169

00:19:34.955 --> 00:19:36.095 And I think this highlights

NOTE Confidence: 0.9607169

00:19:36.395 --> 00:19:38.160 the clear variability in the

NOTE Confidence: 0.9607169

00:19:38.160 --> 00:19:40.560 severity of disease even, among

NOTE Confidence: 0.9607169

00:19:40.560 --> 00:19:41.760 patients who have the same,

NOTE Confidence: 0.9607169

00:19:41.760 --> 00:19:43.280 for instance, gene or even

NOTE Confidence: 0.9607169

00:19:43.280 --> 00:19:43.780 variants,

NOTE Confidence: 0.9477605

00:19:44.480 --> 00:19:44.980 change.

NOTE Confidence: 0.9784325

00:19:45.920 --> 00:19:47.280 So I mentioned twenty percent

NOTE Confidence: 0.9784325

00:19:47.280 --> 00:19:47.780 heritable,

NOTE Confidence: 0.76708555

00:19:48.320 --> 00:19:48.820 genes.

NOTE Confidence: 0.9822203

00:19:49.280 --> 00:19:50.480 Twenty percent of the disease

NOTE Confidence: 0.9822203

00:19:50.480 --> 00:19:51.940 can be associated with heritable,

NOTE Confidence: 0.98233193

00:19:52.424 --> 00:19:54.505 conditions. There's also been recent

NOTE Confidence: 0.98233193

00:19:54.505 --> 00:19:56.205 data to try to understand

NOTE Confidence: 0.9923228

00:19:56.984 --> 00:19:58.684 aortic dilation and aneurysm

NOTE Confidence: 0.9353193

00:19:59.304 --> 00:20:00.505 in the sense of a

NOTE Confidence: 0.9353193

00:20:00.505 --> 00:20:01.484 complex disease.

NOTE Confidence: 0.87617844

00:20:02.105 --> 00:20:03.225 And so GWAS studies have

NOTE Confidence: 0.87617844

00:20:03.225 --> 00:20:03.884 been conducted

NOTE Confidence: 0.92822486

00:20:05.225 --> 00:20:07.164 using UK Biobank data

NOTE Confidence: 0.96885693

00:20:07.700 --> 00:20:09.780 and associating that with ascending

NOTE Confidence: 0.96885693

00:20:09.780 --> 00:20:11.880 aorta diameter values on MRIs

NOTE Confidence: 0.96885693

00:20:11.940 --> 00:20:13.140 and, you know, eighty two

NOTE Confidence: 0.96885693

00:20:13.140 --> 00:20:15.080 GWAS loci were were identified.

NOTE Confidence: 0.9966341

00:20:15.700 --> 00:20:16.200 Likewise,

NOTE Confidence: 0.9161188

00:20:16.900 --> 00:20:18.420 a large study of eight

NOTE Confidence: 0.9161188

00:20:18.420 --> 00:20:20.580 thousand TA dissection cases compared

NOTE Confidence: 0.9161188

00:20:20.580 --> 00:20:22.040 to four hundred fifty thousand

NOTE Confidence: 0.48057327

00:20:22.420 --> 00:20:22.920 non

NOTE Confidence: 0.89964074

00:20:23.355 --> 00:20:25.535 thoracic aortic aneurysm dissection cases,

NOTE Confidence: 0.96289796

00:20:25.915 --> 00:20:27.434 in the million veterans program

NOTE Confidence: 0.96289796

00:20:27.434 --> 00:20:28.734 identified twenty one,

NOTE Confidence: 0.9803671

00:20:29.755 --> 00:20:31.135 loci that were associated

NOTE Confidence: 0.9865215

00:20:31.595 --> 00:20:32.255 with disease.

NOTE Confidence: 0.9869024

00:20:32.715 --> 00:20:33.835 So trying to put together

NOTE Confidence: 0.9869024

00:20:33.835 --> 00:20:34.734 maybe a polygenic

NOTE Confidence: 0.99979407

00:20:35.035 --> 00:20:35.535 contribution

NOTE Confidence: 0.89390826

00:20:36.270 --> 00:20:37.010 to disease,

NOTE Confidence: 0.98585176

00:20:37.390 --> 00:20:39.330 either development or or progression.

NOTE Confidence: 0.8642893

00:20:40.270 --> 00:20:41.869 And so as doctor Aznes,

NOTE Confidence: 0.97553617

00:20:42.190 --> 00:20:44.030 alluded to, you know, my

NOTE Confidence: 0.97553617

00:20:44.030 --> 00:20:45.710 research has has tried to

NOTE Confidence: 0.97553617

00:20:45.710 --> 00:20:47.710 utilize human samples in order

NOTE Confidence: 0.97553617

00:20:47.710 --> 00:20:49.125 to ask questions that are

NOTE Confidence: 0.97553617

00:20:49.125 --> 00:20:50.025 clinically relevant.

NOTE Confidence: 0.9619097

00:20:50.484 --> 00:20:51.845 In order to to pursue

NOTE Confidence: 0.9619097

00:20:51.845 --> 00:20:54.244 this, we developed this, study

NOTE Confidence: 0.9619097

00:20:54.244 --> 00:20:56.105 in which, we enroll participants,

NOTE Confidence: 0.9619097

00:20:56.325 --> 00:20:57.865 collect comprehensive data.

NOTE Confidence: 0.8653594

00:20:58.325 --> 00:20:59.845 When the needing an aortic

NOTE Confidence: 0.8653594

00:20:59.845 --> 00:21:00.984 surgery, we collected,

NOTE Confidence: 0.9715976

00:21:01.445 --> 00:21:03.309 aortic tissue and processed in

NOTE Confidence: 0.9715976

00:21:03.309 --> 00:21:04.289 many ways, including,

NOTE Confidence: 0.89738727

00:21:04.830 --> 00:21:05.330 specimens,

NOTE Confidence: 0.7951744

00:21:06.510 --> 00:21:07.570 processed for histology,

NOTE Confidence: 0.6921119

00:21:08.029 --> 00:21:08.669 electron micro

NOTE Confidence: 0.99343234

00:21:09.230 --> 00:21:09.730 microscopy,

NOTE Confidence: 0.927547

00:21:10.109 --> 00:21:10.929 flash freezing,

NOTE Confidence: 0.9856949

00:21:11.309 --> 00:21:13.309 and we also cultured primary

NOTE Confidence: 0.9856949

00:21:13.309 --> 00:21:14.684 smooth muscle cells directly from

NOTE Confidence: 0.9856949

00:21:14.684 --> 00:21:16.205 the aorta using an explant

NOTE Confidence: 0.9856949

00:21:16.205 --> 00:21:18.044 outgrowth method and then extracted

NOTE Confidence: 0.9856949

00:21:18.044 --> 00:21:19.325 RNA and protein at early

NOTE Confidence: 0.9856949

00:21:19.325 --> 00:21:19.825 passage.

NOTE Confidence: 0.9937075

00:21:20.445 --> 00:21:21.484 In addition to that, all

NOTE Confidence: 0.9937075

00:21:21.484 --> 00:21:21.984 participants,

NOTE Confidence: 0.9729242

00:21:22.684 --> 00:21:23.804 would provide a blood sample,

NOTE Confidence: 0.9729242

00:21:23.804 --> 00:21:25.325 and we have processed those

NOTE Confidence: 0.9729242

00:21:25.325 --> 00:21:27.345 broadly as well for transcriptome,

NOTE Confidence: 0.6148684

00:21:28.684 --> 00:21:28.890 you

NOTE Confidence: 0.92496705

00:21:29.930 --> 00:21:32.250 DNA extraction, plasma studies, as

NOTE Confidence: 0.92496705

00:21:32.250 --> 00:21:33.770 well as, frozen aliquots of

NOTE Confidence: 0.92496705

00:21:33.770 --> 00:21:34.510 whole blood.

NOTE Confidence: 0.9606664

00:21:35.930 --> 00:21:38.410 So, success was was, kinda

NOTE Confidence: 0.9606664

00:21:38.410 --> 00:21:39.690 indicated by the large number

NOTE Confidence: 0.9606664

00:21:39.690 --> 00:21:40.890 of patients. We have enrolled

NOTE Confidence: 0.9606664

00:21:40.890 --> 00:21:42.030 over fourteen hundred,

NOTE Confidence: 0.9837605

00:21:42.685 --> 00:21:44.445 collected aortic tissue samples from

NOTE Confidence: 0.9837605

00:21:44.445 --> 00:21:46.145 greater than four hundred individuals.

NOTE Confidence: 0.99336845

00:21:46.845 --> 00:21:48.545 This includes cases and controls,

NOTE Confidence: 0.9967396

00:21:49.165 --> 00:21:50.465 undergoing a heart transplant

NOTE Confidence: 0.9631943

00:21:51.484 --> 00:21:53.325 or or, organ donors. And

NOTE Confidence: 0.9631943

00:21:53.325 --> 00:21:54.525 then we cultured smooth muscle

NOTE Confidence: 0.9631943

00:21:54.525 --> 00:21:55.725 cells from greater from over

NOTE Confidence: 0.9631943

00:21:55.725 --> 00:21:57.025 a hundred, individuals.

NOTE Confidence: 0.9703065

00:21:58.390 --> 00:22:00.150 And so, I mentioned before

NOTE Confidence: 0.9703065

00:22:00.150 --> 00:22:01.290 that, the,

NOTE Confidence: 0.98927104

00:22:02.150 --> 00:22:03.429 effect of an FBN one

NOTE Confidence: 0.98927104

00:22:03.429 --> 00:22:05.609 variant may have clinical significance

NOTE Confidence: 0.841753

00:22:05.990 --> 00:22:06.970 on course,

NOTE Confidence: 0.97952753

00:22:07.990 --> 00:22:09.270 in patients who have Marfan

NOTE Confidence: 0.97952753

00:22:09.270 --> 00:22:10.710 syndrome. And so we conducted

NOTE Confidence: 0.97952753

00:22:10.710 --> 00:22:11.984 a study in which we,

NOTE Confidence: 0.94967926

00:22:12.625 --> 00:22:13.905 try to utilize the patient's

NOTE Confidence: 0.94967926

00:22:13.905 --> 00:22:15.345 own samples in order to

NOTE Confidence: 0.94967926

00:22:15.345 --> 00:22:17.505 understand the transcriptional effects of

NOTE Confidence: 0.94967926

00:22:17.505 --> 00:22:19.125 FBN one variance. And so,

NOTE Confidence: 0.94967926

00:22:19.424 --> 00:22:20.865 we we studied in this

NOTE Confidence: 0.94967926

00:22:20.865 --> 00:22:22.625 here, twelve patients, five with

NOTE Confidence: 0.94967926

00:22:22.625 --> 00:22:24.325 Marfan syndrome and seven controls,

NOTE Confidence: 0.8913546

00:22:25.210 --> 00:22:26.970 collected a blood sample for

NOTE Confidence: 0.8913546

00:22:26.970 --> 00:22:28.110 whole genome sequencing,

NOTE Confidence: 0.92588776

00:22:28.650 --> 00:22:29.530 and then we cultured the

NOTE Confidence: 0.92588776

00:22:29.530 --> 00:22:31.050 smooth muscle cells and did

NOTE Confidence: 0.92588776

00:22:31.050 --> 00:22:32.110 mRNA sequencing,

NOTE Confidence: 0.9378792

00:22:32.890 --> 00:22:35.630 at greater than, typical depths.

NOTE Confidence: 0.8723172

00:22:36.170 --> 00:22:37.370 We we attempted, and then

NOTE Confidence: 0.8723172

00:22:37.370 --> 00:22:38.145 we sought to integrate

NOTE Confidence: 0.9519719

00:22:39.345 --> 00:22:41.105 understand the transcriptional effects of

NOTE Confidence: 0.9519719

00:22:41.105 --> 00:22:41.765 the variance.

NOTE Confidence: 0.94393015

00:22:42.385 --> 00:22:43.585 You can see that relatively

NOTE Confidence: 0.94393015

00:22:43.585 --> 00:22:45.185 young patients with Marfan syndrome

NOTE Confidence: 0.94393015

00:22:45.185 --> 00:22:46.305 and the and the controls

NOTE Confidence: 0.94393015

00:22:46.305 --> 00:22:46.965 were reasonably,

NOTE Confidence: 0.94128907

00:22:47.505 --> 00:22:48.805 matched to age as well.

NOTE Confidence: 0.94128907

00:22:48.945 --> 00:22:50.480 And so, one of the

NOTE Confidence: 0.94128907

00:22:50.480 --> 00:22:51.280 things we did, we first

NOTE Confidence: 0.94128907

00:22:51.280 --> 00:22:53.359 had mRNA seek, data. And

NOTE Confidence: 0.94128907

00:22:53.359 --> 00:22:54.320 so we asked the question

NOTE Confidence: 0.94128907

00:22:54.320 --> 00:22:55.520 of whether we could identify

NOTE Confidence: 0.94128907

00:22:55.520 --> 00:22:57.680 pathogenic variants directly from sequencing

NOTE Confidence: 0.94128907

00:22:57.680 --> 00:22:59.200 of the mRNA seek reads.

NOTE Confidence: 0.94128907

00:22:59.200 --> 00:23:00.900 And indeed indeed, we did,

NOTE Confidence: 0.95969975

00:23:01.359 --> 00:23:02.400 and then we confirmed these

NOTE Confidence: 0.95969975

00:23:02.400 --> 00:23:03.540 with genome sequencing.

NOTE Confidence: 0.9970771

00:23:04.105 --> 00:23:05.065 And we wanted to use

NOTE Confidence: 0.9970771

00:23:05.065 --> 00:23:06.984 that data also to understand

NOTE Confidence: 0.9970771

00:23:06.984 --> 00:23:08.265 what is the functional effect

NOTE Confidence: 0.9970771

00:23:08.265 --> 00:23:09.164 on the transcript.

NOTE Confidence: 0.9476758

00:23:09.544 --> 00:23:10.904 So, what we observed was

NOTE Confidence: 0.9476758

00:23:10.904 --> 00:23:11.784 that in the patients who

NOTE Confidence: 0.9476758

00:23:11.784 --> 00:23:12.924 had non synonymous,

NOTE Confidence: 0.9063152

00:23:13.304 --> 00:23:14.825 single nucleotide variants that the

NOTE Confidence: 0.9063152

00:23:14.825 --> 00:23:16.505 fraction of the alternative allele

NOTE Confidence: 0.9063152

00:23:16.505 --> 00:23:18.210 reads in the mRNA seek

NOTE Confidence: 0.9063152

00:23:18.210 --> 00:23:19.410 data was similar to to

NOTE Confidence: 0.9063152

00:23:19.410 --> 00:23:20.150 the reference,

NOTE Confidence: 0.9441898

00:23:20.770 --> 00:23:21.270 whereas,

NOTE Confidence: 0.93915105

00:23:21.730 --> 00:23:22.609 in a patient who had

NOTE Confidence: 0.93915105

00:23:22.609 --> 00:23:23.650 a stop gain variant, we

NOTE Confidence: 0.93915105

00:23:23.650 --> 00:23:24.470 saw a decrease,

NOTE Confidence: 0.9918116

00:23:24.850 --> 00:23:26.150 in the fraction of reads,

NOTE Confidence: 0.9844225

00:23:26.930 --> 00:23:28.369 with the alternative allele in

NOTE Confidence: 0.9844225

00:23:28.369 --> 00:23:30.150 that patient's smooth muscle cells,

NOTE Confidence: 0.8741598

00:23:30.530 --> 00:23:32.244 indicating likely non sense media

NOTE Confidence: 0.8741598

00:23:32.244 --> 00:23:32.744 decay.

NOTE Confidence: 0.94372356

00:23:33.684 --> 00:23:34.804 Amongst the data was also

NOTE Confidence: 0.94372356

00:23:34.804 --> 00:23:36.885 we identified a, deletion in

NOTE Confidence: 0.94372356

00:23:36.885 --> 00:23:38.325 exon forty seven in one

NOTE Confidence: 0.94372356

00:23:38.325 --> 00:23:38.825 patient,

NOTE Confidence: 0.92647547

00:23:39.525 --> 00:23:40.484 and in in trying to

NOTE Confidence: 0.92647547

00:23:40.484 --> 00:23:41.924 understand what was the, effect

NOTE Confidence: 0.92647547

00:23:41.924 --> 00:23:43.525 of allelic transcription on this

NOTE Confidence: 0.92647547

00:23:43.525 --> 00:23:44.645 individual. You can see that

NOTE Confidence: 0.92647547

00:23:44.645 --> 00:23:45.225 the number

NOTE Confidence: 0.98305213

00:23:45.525 --> 00:23:47.630 of reads that overlapped the

NOTE Confidence: 0.98305213

00:23:47.630 --> 00:23:49.650 normal exon exon junctions,

NOTE Confidence: 0.99159884

00:23:50.109 --> 00:23:51.710 was relatively similar to the

NOTE Confidence: 0.99159884

00:23:51.710 --> 00:23:53.150 number of reads that aligned

NOTE Confidence: 0.99159884

00:23:53.150 --> 00:23:54.210 over the abnormal,

NOTE Confidence: 0.9121267

00:23:54.669 --> 00:23:55.970 exon exon junctions,

NOTE Confidence: 0.94563675

00:23:56.350 --> 00:23:58.510 again, suggesting that this, variant

NOTE Confidence: 0.94563675

00:23:58.510 --> 00:23:59.494 did not lead to

NOTE Confidence: 0.9541364

00:24:00.035 --> 00:24:00.195 significant,

NOTE Confidence: 0.9461604

00:24:01.075 --> 00:24:01.575 pretranslational

NOTE Confidence: 0.9447333

00:24:02.355 --> 00:24:03.494 transcriptional abnormality.

NOTE Confidence: 0.98383087

00:24:04.355 --> 00:24:06.455 We further explored allelic expression

NOTE Confidence: 0.98383087

00:24:06.675 --> 00:24:07.895 in in these samples.

NOTE Confidence: 0.93652236

00:24:08.275 --> 00:24:10.195 Here, we've plotted across all

NOTE Confidence: 0.93652236

00:24:10.195 --> 00:24:10.935 all samples,

NOTE Confidence: 0.93986404

00:24:11.570 --> 00:24:13.590 the single the single nucleotide

NOTE Confidence: 0.93986404

00:24:13.650 --> 00:24:15.170 variants that were identified. And

NOTE Confidence: 0.93986404

00:24:15.170 --> 00:24:16.369 we're graphing here the fraction

NOTE Confidence: 0.93986404

00:24:16.369 --> 00:24:17.510 of reads with the alternative

NOTE Confidence: 0.93986404

00:24:17.570 --> 00:24:19.010 allele, and then we've labeled,

NOTE Confidence: 0.93986404

00:24:19.250 --> 00:24:20.530 according to samples. So some

NOTE Confidence: 0.93986404

00:24:20.530 --> 00:24:22.230 patients would have multiple snips,

NOTE Confidence: 0.9750294

00:24:22.530 --> 00:24:23.410 in this gene, and then

NOTE Confidence: 0.9750294

00:24:23.410 --> 00:24:24.210 we can look at what

NOTE Confidence: 0.9750294

00:24:24.210 --> 00:24:25.715 the proportion of reads are.

NOTE Confidence: 0.9750294

00:24:25.715 --> 00:24:26.355 And you can see that

NOTE Confidence: 0.9750294

00:24:26.355 --> 00:24:27.155 for the patient who had

NOTE Confidence: 0.9750294

00:24:27.155 --> 00:24:27.815 the nonsense,

NOTE Confidence: 0.969164

00:24:28.515 --> 00:24:30.455 who had the, nonsense variant,

NOTE Confidence: 0.86690366

00:24:31.075 --> 00:24:31.575 we,

NOTE Confidence: 0.8927253

00:24:32.115 --> 00:24:33.475 observe that in all for

NOTE Confidence: 0.8927253

00:24:33.475 --> 00:24:34.835 all SNPs, a skewing of

NOTE Confidence: 0.8927253

00:24:34.835 --> 00:24:36.295 the, of the ratio,

NOTE Confidence: 0.9333696

00:24:36.632 --> 00:24:37.710 of the of the fraction

NOTE Confidence: 0.9333696

00:24:37.710 --> 00:24:38.830 of reads with the alternative

NOTE Confidence: 0.9333696

00:24:38.830 --> 00:24:41.230 allele, again, adding additional support

NOTE Confidence: 0.9333696

00:24:41.230 --> 00:24:41.890 to the,

NOTE Confidence: 0.9491615

00:24:42.350 --> 00:24:44.210 likelihood of nonsense mediated decay.

NOTE Confidence: 0.9491615

00:24:44.270 --> 00:24:45.150 In addition to that, I

NOTE Confidence: 0.9491615

00:24:45.150 --> 00:24:46.850 would suggest that we're detecting

NOTE Confidence: 0.9835749

00:24:47.150 --> 00:24:47.390 the,

NOTE Confidence: 0.9194821

00:24:48.510 --> 00:24:49.730 what is a truncated

NOTE Confidence: 0.9767774

00:24:51.775 --> 00:24:52.275 allele

NOTE Confidence: 0.6751036

00:24:52.734 --> 00:24:53.234 transcript.

NOTE Confidence: 0.99861693

00:24:53.855 --> 00:24:54.655 And, you know, I think

NOTE Confidence: 0.99861693

00:24:54.655 --> 00:24:56.015 we're suggesting that, you know,

NOTE Confidence: 0.99861693

00:24:56.015 --> 00:24:57.234 this isn't necessarily

NOTE Confidence: 0.96909446

00:24:57.695 --> 00:24:59.615 rapidly degraded and maybe could

NOTE Confidence: 0.96909446

00:24:59.615 --> 00:25:00.734 have a combination of a

NOTE Confidence: 0.96909446

00:25:00.734 --> 00:25:01.234 haploinsufficiency

NOTE Confidence: 0.9805559

00:25:02.175 --> 00:25:03.535 as well as potentially dominant

NOTE Confidence: 0.9805559

00:25:03.535 --> 00:25:04.975 negative effects if that transcript

NOTE Confidence: 0.9805559

00:25:04.975 --> 00:25:06.280 goes on to translation, for

NOTE Confidence: 0.9805559

00:25:06.280 --> 00:25:06.780 example.

NOTE Confidence: 0.9381026

00:25:07.240 --> 00:25:08.200 We looked at the gene

NOTE Confidence: 0.9381026

00:25:08.200 --> 00:25:09.720 expression level overall. And, again,

NOTE Confidence: 0.9381026

00:25:09.720 --> 00:25:10.440 with the patient who had

NOTE Confidence: 0.9381026

00:25:10.440 --> 00:25:11.880 nonsense median decay, we saw

NOTE Confidence: 0.9381026

00:25:11.880 --> 00:25:13.400 a low level of FBN

NOTE Confidence: 0.9381026

00:25:13.400 --> 00:25:14.760 one relative to controls in

NOTE Confidence: 0.9381026

00:25:14.760 --> 00:25:16.040 other in the majority of

NOTE Confidence: 0.9381026

00:25:16.040 --> 00:25:16.780 other cases.

NOTE Confidence: 0.99846303

00:25:17.240 --> 00:25:17.740 Again,

NOTE Confidence: 0.9447325

00:25:18.119 --> 00:25:19.375 indicating that, you know, in

NOTE Confidence: 0.9447325

00:25:19.375 --> 00:25:21.315 this patient, there wasn't, inadequate,

NOTE Confidence: 0.9927333

00:25:21.615 --> 00:25:22.835 for example, compensatory

NOTE Confidence: 0.9613183

00:25:23.135 --> 00:25:24.975 increase in expression of the

NOTE Confidence: 0.9613183

00:25:24.975 --> 00:25:25.955 reference allele.

NOTE Confidence: 0.9482748

00:25:26.655 --> 00:25:27.934 And and and so we've

NOTE Confidence: 0.9482748

00:25:27.934 --> 00:25:29.715 kind of more completely characterized

NOTE Confidence: 0.9482748

00:25:29.775 --> 00:25:31.955 this patient's and others' transcriptional

NOTE Confidence: 0.9482748

00:25:32.095 --> 00:25:33.800 effects using this. And so,

NOTE Confidence: 0.9482748

00:25:33.800 --> 00:25:34.680 you know, this is kind

NOTE Confidence: 0.9482748

00:25:34.680 --> 00:25:35.980 of a test case example.

NOTE Confidence: 0.999579

00:25:36.359 --> 00:25:37.640 I see an opportunity for

NOTE Confidence: 0.999579

00:25:37.640 --> 00:25:39.000 us to utilize these types

NOTE Confidence: 0.999579

00:25:39.000 --> 00:25:40.460 of techniques in order to

NOTE Confidence: 0.8641963

00:25:41.320 --> 00:25:43.500 improve our clinical diagnostic pipelines,

NOTE Confidence: 0.9049201

00:25:44.200 --> 00:25:45.340 when cells

NOTE Confidence: 0.954389

00:25:45.640 --> 00:25:47.500 and and, and DNA

NOTE Confidence: 0.944078

00:25:48.015 --> 00:25:49.455 is available in order to

NOTE Confidence: 0.944078

00:25:49.455 --> 00:25:50.734 to look at FBN one

NOTE Confidence: 0.944078

00:25:50.734 --> 00:25:51.775 genes as well as improve

NOTE Confidence: 0.944078

00:25:51.775 --> 00:25:53.695 our, interpretation of variants and

NOTE Confidence: 0.944078

00:25:53.695 --> 00:25:55.535 other, single gene causes of

NOTE Confidence: 0.944078

00:25:55.535 --> 00:25:56.035 aortopathies.

NOTE Confidence: 0.9833434

00:25:57.615 --> 00:25:58.575 In these data, we did

NOTE Confidence: 0.9833434

00:25:58.575 --> 00:25:59.635 a differential expression

NOTE Confidence: 0.96439636

00:25:59.950 --> 00:26:01.310 analysis of Marfan syndrome compared

NOTE Confidence: 0.96439636

00:26:01.310 --> 00:26:02.050 with controls.

NOTE Confidence: 0.98563194

00:26:02.350 --> 00:26:03.310 We saw an enrichment of

NOTE Confidence: 0.98563194

00:26:03.310 --> 00:26:04.609 genes important for glycerophospholipid

NOTE Confidence: 0.8900598

00:26:05.710 --> 00:26:06.210 metabolism,

NOTE Confidence: 0.8812925

00:26:07.470 --> 00:26:09.250 and, and and and, specifically,

NOTE Confidence: 0.9983544

00:26:10.190 --> 00:26:11.470 genes that are important for

NOTE Confidence: 0.9983544

00:26:11.470 --> 00:26:11.970 the

NOTE Confidence: 0.8541664

00:26:14.555 --> 00:26:17.095 generation and processing of of

NOTE Confidence: 0.8541664

00:26:17.195 --> 00:26:17.775 of lysophosphatidic

NOTE Confidence: 0.8917823

00:26:18.395 --> 00:26:19.775 acid, a fatty acid.

NOTE Confidence: 0.8626771

00:26:20.315 --> 00:26:21.675 And what we observed here

NOTE Confidence: 0.8626771

00:26:21.675 --> 00:26:23.535 is a pattern in which

NOTE Confidence: 0.9475639

00:26:24.234 --> 00:26:25.675 the genes that lead to

NOTE Confidence: 0.9475639

00:26:25.675 --> 00:26:26.175 LPA,

NOTE Confidence: 0.8250575

00:26:26.555 --> 00:26:27.295 so lysophosphatidic

NOTE Confidence: 0.9894352

00:26:27.820 --> 00:26:28.480 acid production

NOTE Confidence: 0.8899911

00:26:28.859 --> 00:26:30.460 were decreased, and those that

NOTE Confidence: 0.8899911

00:26:30.460 --> 00:26:31.359 converted lysophosphatidic

NOTE Confidence: 0.9874657

00:26:31.900 --> 00:26:32.880 acid to phosphatidic

NOTE Confidence: 0.9337451

00:26:33.180 --> 00:26:34.700 acid was increased. So this

NOTE Confidence: 0.9337451

00:26:34.700 --> 00:26:36.540 is some preliminary data suggesting

NOTE Confidence: 0.9337451

00:26:36.540 --> 00:26:38.960 potentially dysregulation of this pathway,

NOTE Confidence: 0.9337451

00:26:39.100 --> 00:26:40.460 specifically in smooth muscle cells

NOTE Confidence: 0.9337451

00:26:40.460 --> 00:26:41.520 and Marfan syndrome.

NOTE Confidence: 0.95172054

00:26:43.145 --> 00:26:45.145 As further exploration in these

NOTE Confidence: 0.95172054

00:26:45.145 --> 00:26:47.164 data, we did single cell

NOTE Confidence: 0.95172054

00:26:47.225 --> 00:26:48.984 gene expression profiling of the

NOTE Confidence: 0.95172054

00:26:48.984 --> 00:26:50.664 cells in culture. So we

NOTE Confidence: 0.95172054

00:26:50.664 --> 00:26:52.024 have always presumed and many

NOTE Confidence: 0.95172054

00:26:52.024 --> 00:26:53.164 have presumed that,

NOTE Confidence: 0.9039661

00:26:53.625 --> 00:26:54.840 the cells that are cultured

NOTE Confidence: 0.9039661

00:26:54.840 --> 00:26:55.799 as in an x plane

NOTE Confidence: 0.9039661

00:26:55.799 --> 00:26:57.720 outgrowth method are smooth muscle

NOTE Confidence: 0.9039661

00:26:57.720 --> 00:26:59.080 cells. So we did single

NOTE Confidence: 0.9039661

00:26:59.080 --> 00:27:01.080 cell profiling and labeling with

NOTE Confidence: 0.9039661

00:27:01.080 --> 00:27:01.980 single r,

NOTE Confidence: 0.8584127

00:27:02.520 --> 00:27:03.900 a computational program

NOTE Confidence: 0.98215896

00:27:04.280 --> 00:27:06.200 confirmed that these these cells

NOTE Confidence: 0.98215896

00:27:06.200 --> 00:27:07.559 do have the characteristics of

NOTE Confidence: 0.98215896

00:27:07.559 --> 00:27:08.919 smooth muscle cells in in

NOTE Confidence: 0.98215896

00:27:08.919 --> 00:27:09.980 four different samples.

NOTE Confidence: 0.94478023

00:27:10.555 --> 00:27:11.994 The pseudo bulk data from

NOTE Confidence: 0.94478023

00:27:11.994 --> 00:27:14.095 the single cell correlated directly

NOTE Confidence: 0.94478023

00:27:14.234 --> 00:27:15.775 with the mRNA seek data,

NOTE Confidence: 0.94478023

00:27:15.994 --> 00:27:17.535 for the gene expression profiling,

NOTE Confidence: 0.980154

00:27:18.234 --> 00:27:20.715 validating this, single cell, fixed

NOTE Confidence: 0.980154

00:27:20.715 --> 00:27:22.315 RNA profiling approach to the

NOTE Confidence: 0.980154

00:27:22.315 --> 00:27:23.295 cultured cells.

NOTE Confidence: 0.97683555

00:27:24.619 --> 00:27:26.380 And then we further delved

NOTE Confidence: 0.97683555

00:27:26.380 --> 00:27:27.580 into the single cell data,

NOTE Confidence: 0.97683555

00:27:27.900 --> 00:27:29.420 thinking about how we may

NOTE Confidence: 0.97683555

00:27:29.420 --> 00:27:30.480 be able to use,

NOTE Confidence: 0.9716845

00:27:31.020 --> 00:27:31.840 cluster analysis,

NOTE Confidence: 0.991857

00:27:32.540 --> 00:27:33.920 in order to subcategorize

NOTE Confidence: 0.99189156

00:27:34.460 --> 00:27:35.980 the expression states of smooth

NOTE Confidence: 0.99189156

00:27:35.980 --> 00:27:37.440 muscle cells in culture,

NOTE Confidence: 0.9118569

00:27:38.140 --> 00:27:39.340 knowing that there is likely

NOTE Confidence: 0.9118569

00:27:39.340 --> 00:27:40.160 to be heterogeneity.

NOTE Confidence: 0.996334

00:27:40.675 --> 00:27:41.715 And then being able to

NOTE Confidence: 0.996334

00:27:41.715 --> 00:27:42.615 look at subpopulations

NOTE Confidence: 0.95226234

00:27:42.915 --> 00:27:44.835 and perform differential expression analysis.

NOTE Confidence: 0.95226234

00:27:44.835 --> 00:27:45.795 And you can see we

NOTE Confidence: 0.95226234

00:27:45.795 --> 00:27:46.295 identified,

NOTE Confidence: 0.9988306

00:27:46.755 --> 00:27:48.135 based on canonical markers,

NOTE Confidence: 0.9908095

00:27:48.675 --> 00:27:50.275 a variety of subtypes of

NOTE Confidence: 0.9908095

00:27:50.275 --> 00:27:51.335 smooth muscle cells,

NOTE Confidence: 0.8740294

00:27:52.515 --> 00:27:54.615 similar proportions between Marfan syndrome

NOTE Confidence: 0.8740294

00:27:54.710 --> 00:27:55.210 controls.

NOTE Confidence: 0.95779216

00:27:55.670 --> 00:27:57.109 We identified a gene called

NOTE Confidence: 0.95779216

00:27:57.109 --> 00:27:58.170 TRPD two,

NOTE Confidence: 0.98237514

00:27:58.550 --> 00:28:00.170 transient receptor potential

NOTE Confidence: 0.5255051

00:28:00.550 --> 00:28:01.050 lineloid

NOTE Confidence: 0.98851174

00:28:01.430 --> 00:28:03.270 two, that was increased in

NOTE Confidence: 0.98851174

00:28:03.270 --> 00:28:05.270 Marfan syndrome compared with controls

NOTE Confidence: 0.98851174

00:28:05.270 --> 00:28:05.930 in this,

NOTE Confidence: 0.9103601

00:28:06.390 --> 00:28:07.830 in the in these, in

NOTE Confidence: 0.9103601

00:28:07.830 --> 00:28:09.369 these, single cell,

NOTE Confidence: 0.9983929

00:28:09.910 --> 00:28:10.410 data

NOTE Confidence: 0.91326404

00:28:10.755 --> 00:28:12.355 and and specifically highest in

NOTE Confidence: 0.91326404

00:28:12.355 --> 00:28:14.135 the genes that were characterized

NOTE Confidence: 0.91326404

00:28:14.195 --> 00:28:15.175 as as contractile.

NOTE Confidence: 0.94510007

00:28:15.875 --> 00:28:16.835 This is a feature plot

NOTE Confidence: 0.94510007

00:28:16.835 --> 00:28:18.115 showing that in general, higher

NOTE Confidence: 0.94510007

00:28:18.115 --> 00:28:19.075 levels of t r p

NOTE Confidence: 0.94510007

00:28:19.075 --> 00:28:19.895 v two expression.

NOTE Confidence: 0.984885

00:28:20.435 --> 00:28:21.795 We then went to the

NOTE Confidence: 0.984885

00:28:21.795 --> 00:28:23.315 tissue, the primary tissue from

NOTE Confidence: 0.984885

00:28:23.315 --> 00:28:24.615 which these cells were cultured

NOTE Confidence: 0.826169

00:28:24.915 --> 00:28:26.275 and and and observed increased

NOTE Confidence: 0.826169

00:28:26.275 --> 00:28:27.790 t TRP v two expression

NOTE Confidence: 0.98793346

00:28:28.170 --> 00:28:29.550 in in in the tissues.

NOTE Confidence: 0.9990276

00:28:29.929 --> 00:28:31.210 We've done a single cell

NOTE Confidence: 0.9990276

00:28:31.210 --> 00:28:32.350 transcriptome analysis

NOTE Confidence: 0.99514323

00:28:32.809 --> 00:28:34.010 of a larger cohort of

NOTE Confidence: 0.99514323

00:28:34.010 --> 00:28:34.750 ten cases.

NOTE Confidence: 0.9493428

00:28:35.609 --> 00:28:36.510 This is primary,

NOTE Confidence: 0.871651

00:28:37.290 --> 00:28:39.130 frozen tissues and five controls

NOTE Confidence: 0.871651

00:28:39.130 --> 00:28:40.410 and also and these data

NOTE Confidence: 0.871651

00:28:40.410 --> 00:28:41.390 showed increased

NOTE Confidence: 0.95003814

00:28:41.924 --> 00:28:42.985 expression of TRPV2.

NOTE Confidence: 0.87173885

00:28:43.524 --> 00:28:44.164 And so what is this

NOTE Confidence: 0.87173885

00:28:44.164 --> 00:28:45.384 gene? It's a mechanosensitive

NOTE Confidence: 0.970145

00:28:46.725 --> 00:28:47.705 calcium permeable

NOTE Confidence: 0.9398803

00:28:48.085 --> 00:28:50.164 channel. Looking in literature about

NOTE Confidence: 0.9398803

00:28:50.164 --> 00:28:51.144 this gene, TRPV1

NOTE Confidence: 0.70841825

00:28:51.445 --> 00:28:52.105 is increased

NOTE Confidence: 0.8652239

00:28:52.565 --> 00:28:55.270 in tissue of Marfan patients

NOTE Confidence: 0.8652239

00:28:55.490 --> 00:28:56.710 in the insomel layer.

NOTE Confidence: 0.93609893

00:28:57.169 --> 00:28:58.530 In a prior report, this

NOTE Confidence: 0.93609893

00:28:58.530 --> 00:28:59.730 gene seems to be important

NOTE Confidence: 0.93609893

00:28:59.730 --> 00:29:01.510 in rats for aortic tone.

NOTE Confidence: 0.93609893

00:29:01.809 --> 00:29:02.710 And then also,

NOTE Confidence: 0.9978133

00:29:03.010 --> 00:29:04.230 this gene is regulated

NOTE Confidence: 0.8268433

00:29:05.169 --> 00:29:05.669 or

NOTE Confidence: 0.9905876

00:29:05.970 --> 00:29:07.030 altered by

NOTE Confidence: 0.99516875

00:29:08.625 --> 00:29:09.125 activation

NOTE Confidence: 0.9938709

00:29:09.585 --> 00:29:10.325 of the lysophosphatidic

NOTE Confidence: 0.99233454

00:29:10.945 --> 00:29:13.125 acid receptor one by lysophosphatidic

NOTE Confidence: 0.8262696

00:29:13.585 --> 00:29:14.805 acid. So potentially

NOTE Confidence: 0.9570302

00:29:15.265 --> 00:29:17.345 observing some connections there. And

NOTE Confidence: 0.9570302

00:29:17.345 --> 00:29:18.465 so I wanted to make

NOTE Confidence: 0.9570302

00:29:18.465 --> 00:29:19.745 a a point about, you

NOTE Confidence: 0.9570302

00:29:19.745 --> 00:29:21.460 know, one aspect of the

NOTE Confidence: 0.9570302

00:29:21.460 --> 00:29:21.960 pathophysiology

NOTE Confidence: 0.9588375

00:29:22.820 --> 00:29:24.200 of aortic aneurysms,

NOTE Confidence: 0.9759343

00:29:24.820 --> 00:29:26.340 and that is oxidative stress.

NOTE Confidence: 0.9759343

00:29:26.340 --> 00:29:27.560 So, there's

NOTE Confidence: 0.93606484

00:29:27.940 --> 00:29:28.440 abundant

NOTE Confidence: 0.9480753

00:29:28.820 --> 00:29:30.420 data and studies in in

NOTE Confidence: 0.9480753

00:29:30.420 --> 00:29:31.460 mouse models as well as

NOTE Confidence: 0.9480753

00:29:31.460 --> 00:29:33.400 in human tissues to indicate

NOTE Confidence: 0.9480753

00:29:33.495 --> 00:29:35.575 that oxidative stress may be

NOTE Confidence: 0.9480753

00:29:35.575 --> 00:29:36.235 a downstream

NOTE Confidence: 0.98909575

00:29:36.535 --> 00:29:38.375 mediator of the pathogenesis or

NOTE Confidence: 0.98909575

00:29:38.375 --> 00:29:39.335 at least involved in the

NOTE Confidence: 0.98909575

00:29:39.335 --> 00:29:39.835 pathogenesis

NOTE Confidence: 0.9959338

00:29:40.615 --> 00:29:41.195 of human

NOTE Confidence: 0.7289857

00:29:41.815 --> 00:29:42.855 and and and animal model

NOTE Confidence: 0.7289857

00:29:42.855 --> 00:29:43.355 TAA.

NOTE Confidence: 0.99856496

00:29:43.735 --> 00:29:45.015 We added to that literature

NOTE Confidence: 0.99856496

00:29:45.015 --> 00:29:45.835 with the largest

NOTE Confidence: 0.93587047

00:29:46.775 --> 00:29:48.440 collection of fixed,

NOTE Confidence: 0.92892826

00:29:49.460 --> 00:29:49.960 tissues,

NOTE Confidence: 0.88807124

00:29:50.340 --> 00:29:51.379 in which we stained for

NOTE Confidence: 0.88807124

00:29:51.379 --> 00:29:52.980 a marker of oxidative stress,

NOTE Confidence: 0.88807124

00:29:52.980 --> 00:29:53.480 nitrotyrosine,

NOTE Confidence: 0.92291546

00:29:54.179 --> 00:29:55.779 and blinded grading of the

NOTE Confidence: 0.92291546

00:29:55.779 --> 00:29:56.279 intensity

NOTE Confidence: 0.9223479

00:29:56.580 --> 00:29:58.360 observed an increase in TAA

NOTE Confidence: 0.9223479

00:29:58.580 --> 00:30:00.120 samples compared with controls.

NOTE Confidence: 0.9616426

00:30:01.139 --> 00:30:02.519 We also used our samples,

NOTE Confidence: 0.89404184

00:30:02.820 --> 00:30:04.375 to look in smooth muscle

NOTE Confidence: 0.89404184

00:30:04.375 --> 00:30:06.455 cells in situ, using electron

NOTE Confidence: 0.89404184

00:30:06.455 --> 00:30:08.555 microscopy and characterize the mitochondria

NOTE Confidence: 0.89404184

00:30:08.775 --> 00:30:10.875 using a semi quantitative score,

NOTE Confidence: 0.9190626

00:30:11.495 --> 00:30:12.875 again, blinded analysis.

NOTE Confidence: 0.9388021

00:30:13.175 --> 00:30:14.455 And we have, for the,

NOTE Confidence: 0.9388021

00:30:14.855 --> 00:30:16.535 ultra structural defects in the

NOTE Confidence: 0.9388021

00:30:16.535 --> 00:30:18.375 mitochondrial cristae. And, again, we

NOTE Confidence: 0.9388021

00:30:18.375 --> 00:30:20.100 saw higher defect scores in

NOTE Confidence: 0.9388021

00:30:20.100 --> 00:30:21.460 TAA for the majority, six

NOTE Confidence: 0.9388021

00:30:21.460 --> 00:30:22.920 out of the seven, cases

NOTE Confidence: 0.9388021

00:30:22.980 --> 00:30:24.680 compared compared with the controls.

NOTE Confidence: 0.98273176

00:30:25.300 --> 00:30:26.820 And most recently, we've looked

NOTE Confidence: 0.98273176

00:30:26.820 --> 00:30:27.320 at

NOTE Confidence: 0.8801294

00:30:27.700 --> 00:30:29.140 a series of cases, who

NOTE Confidence: 0.8801294

00:30:29.140 --> 00:30:29.880 had TAA,

NOTE Confidence: 0.8464397

00:30:30.420 --> 00:30:31.960 did on targeted metabolomics,

NOTE Confidence: 0.8976878

00:30:32.295 --> 00:30:32.795 and

NOTE Confidence: 0.9050758

00:30:33.255 --> 00:30:34.795 and compared those two controls.

NOTE Confidence: 0.9050758

00:30:34.935 --> 00:30:36.455 These are relatively young patients,

NOTE Confidence: 0.9050758

00:30:36.455 --> 00:30:37.755 average age in the thirties,

NOTE Confidence: 0.8555429

00:30:38.375 --> 00:30:39.895 and we're observing in this

NOTE Confidence: 0.8555429

00:30:39.895 --> 00:30:41.655 amongst these data, we we

NOTE Confidence: 0.8555429

00:30:41.655 --> 00:30:42.155 saw,

NOTE Confidence: 0.9247321

00:30:42.615 --> 00:30:43.815 a decrease in the ratio

NOTE Confidence: 0.9247321

00:30:43.815 --> 00:30:45.160 of reduced glutathione to to

NOTE Confidence: 0.9247321

00:30:45.160 --> 00:30:46.540 oxidized glutathione disulfide.

NOTE Confidence: 0.9725894

00:30:46.920 --> 00:30:48.520 Again, another marker of oxidative

NOTE Confidence: 0.9725894

00:30:48.520 --> 00:30:49.720 stress. So I think trying

NOTE Confidence: 0.9725894

00:30:49.720 --> 00:30:51.080 to paint a picture here

NOTE Confidence: 0.9725894

00:30:51.080 --> 00:30:51.820 and and,

NOTE Confidence: 0.9711182

00:30:52.680 --> 00:30:54.380 and and thinking about oxidative

NOTE Confidence: 0.9711182

00:30:54.440 --> 00:30:55.820 stress as a prevalent,

NOTE Confidence: 0.8958684

00:30:57.000 --> 00:30:58.220 aspect of the pathophysiology,

NOTE Confidence: 0.78359395

00:30:59.093 --> 00:30:59.660 including across, different etiologies, which,

NOTE Confidence: 0.78356826

00:31:02.775 --> 00:31:03.415 different etiologies, which, these these,

NOTE Confidence: 0.84633416

00:31:04.455 --> 00:31:06.934 these samples consisted of. And

NOTE Confidence: 0.84633416

00:31:06.934 --> 00:31:07.434 so,

NOTE Confidence: 0.958499

00:31:08.135 --> 00:31:09.575 you know, as I pointed

NOTE Confidence: 0.958499

00:31:09.575 --> 00:31:10.455 to in the,

NOTE Confidence: 0.92156094

00:31:11.015 --> 00:31:12.535 Kaplan Meier type curves that

NOTE Confidence: 0.92156094

00:31:12.535 --> 00:31:13.995 we observe with genes,

NOTE Confidence: 0.837351

00:31:14.455 --> 00:31:16.059 and variance in gene types,

NOTE Confidence: 0.93388903

00:31:16.360 --> 00:31:18.059 you know, there is substantial

NOTE Confidence: 0.93388903

00:31:18.200 --> 00:31:19.500 inter individual variability

NOTE Confidence: 0.97934204

00:31:19.800 --> 00:31:21.080 in the progression and the

NOTE Confidence: 0.97934204

00:31:21.080 --> 00:31:22.220 outcomes in patients.

NOTE Confidence: 0.93546534

00:31:22.760 --> 00:31:23.720 We looked at in the

NOTE Confidence: 0.93546534

00:31:23.720 --> 00:31:25.320 young. So so in children,

NOTE Confidence: 0.93546534

00:31:25.320 --> 00:31:26.059 we echocardiography

NOTE Confidence: 0.9590185

00:31:26.360 --> 00:31:27.320 is the standard way we

NOTE Confidence: 0.9590185

00:31:27.320 --> 00:31:28.620 monitor them, and we calculate

NOTE Confidence: 0.9590185

00:31:28.840 --> 00:31:30.360 a z score to index

NOTE Confidence: 0.9590185

00:31:30.360 --> 00:31:30.860 their

NOTE Confidence: 0.9953527

00:31:31.205 --> 00:31:32.645 diameter to body size in

NOTE Confidence: 0.9953527

00:31:32.645 --> 00:31:33.845 order to grade whether there's

NOTE Confidence: 0.9953527

00:31:33.845 --> 00:31:34.345 dilation

NOTE Confidence: 0.97522867

00:31:34.645 --> 00:31:34.965 or

NOTE Confidence: 0.92974716

00:31:35.605 --> 00:31:37.365 and present, and if present,

NOTE Confidence: 0.92974716

00:31:37.365 --> 00:31:38.345 how severe.

NOTE Confidence: 0.96487695

00:31:38.885 --> 00:31:40.185 And we looked at retrospectively

NOTE Confidence: 0.96487695

00:31:40.405 --> 00:31:41.285 at a large group of

NOTE Confidence: 0.96487695

00:31:41.525 --> 00:31:43.065 relatively large group of patients,

NOTE Confidence: 0.95182234

00:31:43.525 --> 00:31:44.485 who were followed for at

NOTE Confidence: 0.95182234

00:31:44.485 --> 00:31:45.830 least five years, and the

NOTE Confidence: 0.95182234

00:31:45.830 --> 00:31:46.570 average follow-up

NOTE Confidence: 0.9322997

00:31:47.270 --> 00:31:48.310 was was ten years. And,

NOTE Confidence: 0.9322997

00:31:48.310 --> 00:31:49.030 you know, I think that

NOTE Confidence: 0.9322997

00:31:49.030 --> 00:31:50.230 this is kind of kind

NOTE Confidence: 0.9322997

00:31:50.230 --> 00:31:50.390 of,

NOTE Confidence: 0.9685577

00:31:51.110 --> 00:31:52.630 a lot of information, right

NOTE Confidence: 0.9685577

00:31:52.630 --> 00:31:53.350 here. But I think what

NOTE Confidence: 0.9685577

00:31:53.350 --> 00:31:54.630 you can see is, a

NOTE Confidence: 0.9685577

00:31:54.630 --> 00:31:55.590 rate of change in z

NOTE Confidence: 0.9685577

00:31:55.590 --> 00:31:57.110 score from baseline to to

NOTE Confidence: 0.9685577

00:31:57.110 --> 00:31:57.610 last

NOTE Confidence: 0.95838976

00:31:58.395 --> 00:31:59.435 of of zero would mean,

NOTE Confidence: 0.95838976

00:31:59.435 --> 00:32:00.715 you know, no no evidence

NOTE Confidence: 0.95838976

00:32:00.715 --> 00:32:01.375 for progression.

NOTE Confidence: 0.95440716

00:32:01.915 --> 00:32:03.195 There's some who improved and

NOTE Confidence: 0.95440716

00:32:03.195 --> 00:32:03.855 some who,

NOTE Confidence: 0.9409058

00:32:04.395 --> 00:32:06.015 who who progressed over time.

NOTE Confidence: 0.9409058

00:32:06.075 --> 00:32:07.195 And and that was highly

NOTE Confidence: 0.9409058

00:32:07.195 --> 00:32:08.795 variable within groups, including, you

NOTE Confidence: 0.9409058

00:32:08.795 --> 00:32:10.475 know, within Marfan, within bicuspid

NOTE Confidence: 0.9409058

00:32:10.475 --> 00:32:11.250 aortic valve patients who

NOTE Confidence: 0.8502144

00:32:14.690 --> 00:32:16.450 variability in pediatric progression of

NOTE Confidence: 0.8502144

00:32:16.450 --> 00:32:16.950 disease.

NOTE Confidence: 0.94752324

00:32:17.890 --> 00:32:19.270 In addition, there's pedigrees,

NOTE Confidence: 0.94577247

00:32:19.810 --> 00:32:21.670 that clearly highlight the intrafamilial

NOTE Confidence: 0.94577247

00:32:21.890 --> 00:32:24.050 variability. So patients who, have

NOTE Confidence: 0.94577247

00:32:24.050 --> 00:32:25.490 the same family members who

NOTE Confidence: 0.94577247

00:32:25.490 --> 00:32:26.790 have the same, pathogenic

NOTE Confidence: 0.9545184

00:32:27.105 --> 00:32:29.505 mutation, quite substantial differences in

NOTE Confidence: 0.9545184

00:32:29.505 --> 00:32:30.785 their outcomes. You know, this

NOTE Confidence: 0.9545184

00:32:30.785 --> 00:32:31.665 is a nice study that

NOTE Confidence: 0.9545184

00:32:31.665 --> 00:32:33.025 they looked at a a

NOTE Confidence: 0.9545184

00:32:33.025 --> 00:32:34.065 a family who had TGF

NOTE Confidence: 0.9545184

00:32:34.065 --> 00:32:35.184 beta r two. And you

NOTE Confidence: 0.9545184

00:32:35.184 --> 00:32:36.065 can see that, you know,

NOTE Confidence: 0.9545184

00:32:36.065 --> 00:32:38.065 there were complications in many,

NOTE Confidence: 0.9545184

00:32:38.065 --> 00:32:39.425 but some lived, you know,

NOTE Confidence: 0.9545184

00:32:39.425 --> 00:32:41.585 to later ages, without aortic

NOTE Confidence: 0.9545184

00:32:41.585 --> 00:32:42.780 events. And so the

NOTE Confidence: 0.9794469

00:32:43.180 --> 00:32:45.200 reasons that underlie this variation

NOTE Confidence: 0.8833149

00:32:45.660 --> 00:32:46.940 is unclear. And so all

NOTE Confidence: 0.8833149

00:32:46.940 --> 00:32:48.060 of this put together when

NOTE Confidence: 0.8833149

00:32:48.060 --> 00:32:49.420 I'm seeing patients is we

NOTE Confidence: 0.8833149

00:32:49.420 --> 00:32:50.300 were thinking about are we

NOTE Confidence: 0.8833149

00:32:50.300 --> 00:32:50.940 going to start a patient

NOTE Confidence: 0.8833149

00:32:50.940 --> 00:32:52.060 on beta blocker or AGTense

NOTE Confidence: 0.8833149

00:32:52.060 --> 00:32:52.960 receptor blocker,

NOTE Confidence: 0.97122806

00:32:53.420 --> 00:32:54.540 which is all we have

NOTE Confidence: 0.97122806

00:32:54.540 --> 00:32:55.980 right now. Are we going

NOTE Confidence: 0.97122806

00:32:55.980 --> 00:32:57.555 to recommend some activity restrictions

NOTE Confidence: 0.97122806

00:32:57.555 --> 00:32:58.995 to prevent their progressive dilation?

NOTE Confidence: 0.97122806

00:32:58.995 --> 00:33:00.115 How frequently are we gonna

NOTE Confidence: 0.97122806

00:33:00.115 --> 00:33:01.235 see them? And so you

NOTE Confidence: 0.97122806

00:33:01.235 --> 00:33:02.355 think about this dial. You

NOTE Confidence: 0.97122806

00:33:02.355 --> 00:33:03.235 know, we have a genetic

NOTE Confidence: 0.97122806

00:33:03.235 --> 00:33:04.435 diagnosis. There's some data that

NOTE Confidence: 0.97122806

00:33:04.435 --> 00:33:05.955 we can, you know, population

NOTE Confidence: 0.97122806

00:33:05.955 --> 00:33:06.455 wide,

NOTE Confidence: 0.9555074

00:33:06.835 --> 00:33:07.495 make some,

NOTE Confidence: 0.9758696

00:33:07.875 --> 00:33:08.935 make some decisions,

NOTE Confidence: 0.87935245

00:33:09.315 --> 00:33:10.275 have some rationale for our

NOTE Confidence: 0.87935245

00:33:10.275 --> 00:33:11.555 decision. But largely, it's a

NOTE Confidence: 0.87935245

00:33:11.555 --> 00:33:12.420 very much a

NOTE Confidence: 0.87544715

00:33:13.140 --> 00:33:14.680 kind of standard approach,

NOTE Confidence: 0.97337514

00:33:15.060 --> 00:33:16.120 that's not individualized.

NOTE Confidence: 0.98931336

00:33:16.420 --> 00:33:17.140 And you can see this

NOTE Confidence: 0.98931336

00:33:17.140 --> 00:33:18.500 gets worse as we're looking

NOTE Confidence: 0.98931336

00:33:18.500 --> 00:33:19.300 at the patients who don't

NOTE Confidence: 0.98931336

00:33:19.300 --> 00:33:20.500 have a genetic diagnosis with

NOTE Confidence: 0.98931336

00:33:20.500 --> 00:33:21.540 no real way to stratify

NOTE Confidence: 0.98931336

00:33:21.540 --> 00:33:22.280 their risk.

NOTE Confidence: 0.993252

00:33:23.060 --> 00:33:24.180 So we thought that maybe

NOTE Confidence: 0.993252

00:33:24.180 --> 00:33:26.100 genetic modifiers could contribute to

NOTE Confidence: 0.993252

00:33:26.100 --> 00:33:26.600 the

NOTE Confidence: 0.9977851

00:33:27.434 --> 00:33:28.495 severity of disease.

NOTE Confidence: 0.9470766

00:33:28.875 --> 00:33:30.154 We did exome sequencing in

NOTE Confidence: 0.9470766

00:33:30.154 --> 00:33:31.595 three different families, first degree

NOTE Confidence: 0.9470766

00:33:31.595 --> 00:33:33.115 relatives who had divergence in

NOTE Confidence: 0.9470766

00:33:33.115 --> 00:33:34.554 their TA severity. And we

NOTE Confidence: 0.9470766

00:33:34.554 --> 00:33:35.674 looked at what variants were

NOTE Confidence: 0.9470766

00:33:35.674 --> 00:33:37.034 different, rare coding variants were

NOTE Confidence: 0.9470766

00:33:37.034 --> 00:33:38.235 different between the patients who

NOTE Confidence: 0.9470766

00:33:38.235 --> 00:33:40.315 had mild phenotype versus severe

NOTE Confidence: 0.9470766

00:33:40.315 --> 00:33:41.140 phenotype when it came to

NOTE Confidence: 0.9470766

00:33:41.140 --> 00:33:41.960 their aorta.

NOTE Confidence: 0.9592463

00:33:42.340 --> 00:33:43.940 We crossed all these variants,

NOTE Confidence: 0.9592463

00:33:44.179 --> 00:33:45.460 across the different pedigrees and

NOTE Confidence: 0.9592463

00:33:45.460 --> 00:33:46.520 found this gene CoQAB,

NOTE Confidence: 0.9743518

00:33:46.980 --> 00:33:48.280 this particular variant,

NOTE Confidence: 0.9175028

00:33:48.660 --> 00:33:50.260 that was present segregating with,

NOTE Confidence: 0.9175028

00:33:50.420 --> 00:33:52.020 with disease severity in all

NOTE Confidence: 0.9175028

00:33:52.020 --> 00:33:52.520 three

NOTE Confidence: 0.98375255

00:33:52.865 --> 00:33:53.365 families.

NOTE Confidence: 0.98518777

00:33:53.825 --> 00:33:54.625 What do we know about

NOTE Confidence: 0.98518777

00:33:54.625 --> 00:33:55.125 CoQAB?

NOTE Confidence: 0.9827222

00:33:55.505 --> 00:33:56.805 It's associated with an autosomal

NOTE Confidence: 0.9827222

00:33:56.945 --> 00:33:57.445 recessive

NOTE Confidence: 0.86538136

00:33:58.465 --> 00:33:59.365 kidney disorder,

NOTE Confidence: 0.900399

00:33:59.825 --> 00:34:01.345 but it's nuclear encoded, translates

NOTE Confidence: 0.900399

00:34:01.345 --> 00:34:02.865 to mitochondria. And there, it's

NOTE Confidence: 0.900399

00:34:02.865 --> 00:34:04.145 important for the synthesis of

NOTE Confidence: 0.900399

00:34:04.145 --> 00:34:05.285 coenzyme Q10.

NOTE Confidence: 0.88461524

00:34:05.585 --> 00:34:06.630 And, of course, coenzyme q

NOTE Confidence: 0.88461524

00:34:06.630 --> 00:34:07.510 ten as a head group

NOTE Confidence: 0.88461524

00:34:07.510 --> 00:34:09.450 and, you know, a isoprenoid,

NOTE Confidence: 0.9501296

00:34:10.230 --> 00:34:10.730 tail.

NOTE Confidence: 0.9612819

00:34:11.030 --> 00:34:13.110 It's important for, mitochondrial electron

NOTE Confidence: 0.9612819

00:34:13.110 --> 00:34:14.790 transport as well as, acts

NOTE Confidence: 0.9612819

00:34:14.790 --> 00:34:16.250 as a lipophilic antioxidant.

NOTE Confidence: 0.85243446

00:34:16.790 --> 00:34:18.090 So, you know, potentially,

NOTE Confidence: 0.9661232

00:34:18.550 --> 00:34:19.670 this gene could be acting

NOTE Confidence: 0.9661232

00:34:19.670 --> 00:34:20.790 in a mechanism of of

NOTE Confidence: 0.9661232

00:34:20.790 --> 00:34:22.364 oxidative stress and and,

NOTE Confidence: 0.8322093

00:34:22.765 --> 00:34:24.065 abnormalities in mitochondrial,

NOTE Confidence: 0.9509444

00:34:25.005 --> 00:34:27.005 function, for example. So, we

NOTE Confidence: 0.9509444

00:34:27.005 --> 00:34:28.045 looked in our smooth muscle

NOTE Confidence: 0.9509444

00:34:28.045 --> 00:34:30.045 cells and identified that, expression

NOTE Confidence: 0.9509444

00:34:30.045 --> 00:34:31.725 of CoQAB was decreased in

NOTE Confidence: 0.9509444

00:34:31.725 --> 00:34:33.025 the small series of patients,

NOTE Confidence: 0.9745422

00:34:33.325 --> 00:34:34.925 in smooth muscle cells. We've

NOTE Confidence: 0.9745422

00:34:34.925 --> 00:34:36.305 later, gone on to

NOTE Confidence: 0.9614984

00:34:36.849 --> 00:34:37.810 observe this in a much

NOTE Confidence: 0.9614984

00:34:37.810 --> 00:34:39.089 larger number of samples using

NOTE Confidence: 0.9614984

00:34:39.089 --> 00:34:40.450 mRNA seek that I'll show

NOTE Confidence: 0.9614984

00:34:40.450 --> 00:34:41.349 in a little bit.

NOTE Confidence: 0.97269905

00:34:42.290 --> 00:34:43.170 And then we did some

NOTE Confidence: 0.97269905

00:34:43.170 --> 00:34:44.369 experiments in which we,

NOTE Confidence: 0.8837353

00:34:45.250 --> 00:34:46.869 knocked down CoQAB expression.

NOTE Confidence: 0.95336723

00:34:47.569 --> 00:34:48.790 You can see that CoQAB

NOTE Confidence: 0.95336723

00:34:49.010 --> 00:34:50.450 localized to mitochondria and that

NOTE Confidence: 0.95336723

00:34:50.450 --> 00:34:51.569 we effectively knocked it down

NOTE Confidence: 0.95336723

00:34:51.569 --> 00:34:53.105 with our siRNA. And we

NOTE Confidence: 0.95336723

00:34:53.105 --> 00:34:54.944 observed, functional changes in the

NOTE Confidence: 0.95336723

00:34:54.944 --> 00:34:56.545 smooth muscle cells, including decreased

NOTE Confidence: 0.95336723

00:34:56.545 --> 00:34:57.444 aerobic respiration,

NOTE Confidence: 0.99687517

00:34:57.905 --> 00:34:58.405 increased

NOTE Confidence: 0.9974997

00:34:58.864 --> 00:34:59.925 oxidative stress,

NOTE Confidence: 0.99732274

00:35:00.385 --> 00:35:01.765 including lipid peroxidation,

NOTE Confidence: 0.9482349

00:35:02.305 --> 00:35:03.285 protein carbonylation,

NOTE Confidence: 0.9910416

00:35:04.385 --> 00:35:05.744 and changes in the expression

NOTE Confidence: 0.9910416

00:35:05.744 --> 00:35:06.944 of genes important for smooth

NOTE Confidence: 0.9910416

00:35:06.944 --> 00:35:09.020 muscle cell function, contractile genes.

NOTE Confidence: 0.9524368

00:35:09.480 --> 00:35:10.600 And then more recently, we've

NOTE Confidence: 0.9524368

00:35:10.600 --> 00:35:11.640 done some experiments where we've

NOTE Confidence: 0.9524368

00:35:11.640 --> 00:35:12.940 knocked down and did mRNA

NOTE Confidence: 0.9524368

00:35:13.080 --> 00:35:14.280 sequencing as well as in

NOTE Confidence: 0.9524368

00:35:14.280 --> 00:35:15.980 the context of additional stressors

NOTE Confidence: 0.9524368

00:35:16.040 --> 00:35:17.560 in order to more completely

NOTE Confidence: 0.9524368

00:35:17.560 --> 00:35:18.760 characterize what's the effect of

NOTE Confidence: 0.9524368

00:35:18.760 --> 00:35:20.200 loss of coQA b and

NOTE Confidence: 0.9524368

00:35:20.200 --> 00:35:21.500 aortic smooth muscle cells.

NOTE Confidence: 0.98756945

00:35:21.975 --> 00:35:23.255 During this time, I we

NOTE Confidence: 0.98756945

00:35:23.255 --> 00:35:24.535 saw a study, that was

NOTE Confidence: 0.98756945

00:35:24.535 --> 00:35:25.435 done in yeast,

NOTE Confidence: 0.8646031

00:35:25.815 --> 00:35:27.035 in in which they expressed

NOTE Confidence: 0.8646031

00:35:27.095 --> 00:35:28.635 a missense snips and constructs.

NOTE Confidence: 0.8646031

00:35:28.855 --> 00:35:29.975 And it was a surprising

NOTE Confidence: 0.8646031

00:35:29.975 --> 00:35:30.475 finding,

NOTE Confidence: 0.968485

00:35:30.775 --> 00:35:32.635 that this particular snip,

NOTE Confidence: 0.9960179

00:35:33.335 --> 00:35:34.315 which is common,

NOTE Confidence: 0.9235794

00:35:34.950 --> 00:35:36.550 was had an association. So

NOTE Confidence: 0.9235794

00:35:36.550 --> 00:35:37.530 specifically, the

NOTE Confidence: 0.95084226

00:35:37.830 --> 00:35:38.790 the the variant that leads

NOTE Confidence: 0.95084226

00:35:38.790 --> 00:35:39.530 to the histidine,

NOTE Confidence: 0.92197764

00:35:40.469 --> 00:35:42.150 residue here was associated with

NOTE Confidence: 0.92197764

00:35:42.150 --> 00:35:44.410 decreased activation activity of the,

NOTE Confidence: 0.7583176

00:35:44.790 --> 00:35:46.230 coQ levels basically. So a

NOTE Confidence: 0.7583176

00:35:46.230 --> 00:35:48.170 complex two three assay measures

NOTE Confidence: 0.7583176

00:35:48.310 --> 00:35:48.810 decreased

NOTE Confidence: 0.92159253

00:35:49.175 --> 00:35:51.015 mitochondrial protein levels and decreased

NOTE Confidence: 0.92159253

00:35:51.015 --> 00:35:53.015 aerobic respiration in yeast. So,

NOTE Confidence: 0.92159253

00:35:53.015 --> 00:35:54.715 potentially a functional common SNP.

NOTE Confidence: 0.92159253

00:35:54.775 --> 00:35:56.614 And so, given our interest

NOTE Confidence: 0.92159253

00:35:56.614 --> 00:35:57.355 in CoQAB,

NOTE Confidence: 0.9190079

00:35:57.895 --> 00:35:58.695 I looked at forty eight

NOTE Confidence: 0.9190079

00:35:58.695 --> 00:36:00.475 patients who had longitudinal aortic

NOTE Confidence: 0.962865

00:36:00.855 --> 00:36:02.455 follow-up and tested using a

NOTE Confidence: 0.962865

00:36:02.455 --> 00:36:04.100 mixed model association for

NOTE Confidence: 0.9193382

00:36:04.800 --> 00:36:06.400 this SNP and the rate

NOTE Confidence: 0.9193382

00:36:06.400 --> 00:36:07.460 of aortic dilation

NOTE Confidence: 0.9552473

00:36:08.000 --> 00:36:09.540 and identified that the genotype

NOTE Confidence: 0.72759545

00:36:10.080 --> 00:36:10.900 of g

NOTE Confidence: 0.9290724

00:36:11.280 --> 00:36:12.739 compared to a was associated

NOTE Confidence: 0.9290724

00:36:12.800 --> 00:36:14.100 with a lower

NOTE Confidence: 0.992427

00:36:14.480 --> 00:36:16.100 rate of aortic dilation.

NOTE Confidence: 0.95569664

00:36:18.895 --> 00:36:20.335 And then also, we looked

NOTE Confidence: 0.95569664

00:36:20.335 --> 00:36:21.935 at a second cohort, a

NOTE Confidence: 0.95569664

00:36:21.935 --> 00:36:23.055 cohort of patients who had

NOTE Confidence: 0.95569664

00:36:23.055 --> 00:36:25.055 early onset aortic dissection and

NOTE Confidence: 0.95569664

00:36:25.055 --> 00:36:26.255 saw the same pattern in

NOTE Confidence: 0.95569664

00:36:26.255 --> 00:36:26.995 which patients,

NOTE Confidence: 0.93589723

00:36:27.375 --> 00:36:28.595 who have the AA,

NOTE Confidence: 0.9290078

00:36:29.535 --> 00:36:31.955 genotype have more significant disease,

NOTE Confidence: 0.9290078

00:36:32.175 --> 00:36:33.719 day aortic dissection compared to

NOTE Confidence: 0.9290078

00:36:33.860 --> 00:36:35.160 those with the g,

NOTE Confidence: 0.9631297

00:36:35.780 --> 00:36:37.000 homozygous g,

NOTE Confidence: 0.99813515

00:36:37.300 --> 00:36:37.800 genotype.

NOTE Confidence: 0.96331817

00:36:38.820 --> 00:36:40.180 From a functional standpoint, I

NOTE Confidence: 0.96331817

00:36:40.180 --> 00:36:41.380 showed some functional data in

NOTE Confidence: 0.96331817

00:36:41.380 --> 00:36:42.920 yeast. We extracted

NOTE Confidence: 0.9322457

00:36:43.540 --> 00:36:45.075 protein from aortic smooth muscle

NOTE Confidence: 0.9322457

00:36:45.155 --> 00:36:46.915 cells at early passage. We

NOTE Confidence: 0.9322457

00:36:46.915 --> 00:36:48.755 genotype patients for this SNP,

NOTE Confidence: 0.9322457

00:36:48.755 --> 00:36:50.055 and then we measured CoQAB

NOTE Confidence: 0.9322457

00:36:50.114 --> 00:36:51.714 levels using a western blot.

NOTE Confidence: 0.9322457

00:36:51.954 --> 00:36:52.994 And we observed the same

NOTE Confidence: 0.9322457

00:36:52.994 --> 00:36:54.435 pattern in which the the

NOTE Confidence: 0.9322457

00:36:54.435 --> 00:36:55.575 patients who were homozygous,

NOTE Confidence: 0.98772657

00:36:56.275 --> 00:36:57.015 for the

NOTE Confidence: 0.95947486

00:36:57.980 --> 00:36:59.900 for this, allele that appears

NOTE Confidence: 0.95947486

00:36:59.900 --> 00:37:01.440 to have a protective effect,

NOTE Confidence: 0.95947486

00:37:01.660 --> 00:37:03.339 we saw higher levels of,

NOTE Confidence: 0.95947486

00:37:03.579 --> 00:37:04.079 CoQAB

NOTE Confidence: 0.9536461

00:37:04.380 --> 00:37:04.880 protein,

NOTE Confidence: 0.98519343

00:37:05.420 --> 00:37:06.400 in those cells.

NOTE Confidence: 0.9452509

00:37:07.020 --> 00:37:08.219 And then we confirmed this

NOTE Confidence: 0.9452509

00:37:08.219 --> 00:37:09.660 again. We did an additional

NOTE Confidence: 0.9452509

00:37:09.660 --> 00:37:10.619 six patients and put it

NOTE Confidence: 0.9452509

00:37:10.619 --> 00:37:11.660 put it all together to

NOTE Confidence: 0.9452509

00:37:11.660 --> 00:37:13.525 show that this gene,

NOTE Confidence: 0.9645729

00:37:14.485 --> 00:37:16.425 this variant, that was associated

NOTE Confidence: 0.9645729

00:37:16.485 --> 00:37:16.985 with

NOTE Confidence: 0.90365285

00:37:18.405 --> 00:37:20.405 less severe disease has higher

NOTE Confidence: 0.90365285

00:37:20.405 --> 00:37:21.385 levels of CoQAB.

NOTE Confidence: 0.8925847

00:37:22.245 --> 00:37:22.905 And so,

NOTE Confidence: 0.9369061

00:37:23.525 --> 00:37:24.725 thinking about how that may

NOTE Confidence: 0.9369061

00:37:24.725 --> 00:37:25.525 have a role in the

NOTE Confidence: 0.9369061

00:37:25.525 --> 00:37:27.065 in in the mechanism oxidative

NOTE Confidence: 0.9369061

00:37:27.285 --> 00:37:28.265 stress and disease.

NOTE Confidence: 0.94047594

00:37:29.180 --> 00:37:30.059 So, this is one data

NOTE Confidence: 0.94047594

00:37:30.059 --> 00:37:31.420 set. We're currently doing a

NOTE Confidence: 0.94047594

00:37:31.420 --> 00:37:32.539 study in which we're enrolling

NOTE Confidence: 0.94047594

00:37:32.539 --> 00:37:33.579 three hundred patients and doing

NOTE Confidence: 0.94047594

00:37:33.579 --> 00:37:34.640 whole genome sequencing.

NOTE Confidence: 0.92158383

00:37:35.019 --> 00:37:36.219 It's a multicenter study and

NOTE Confidence: 0.92158383

00:37:36.219 --> 00:37:37.200 we're going to be investigating

NOTE Confidence: 0.92158383

00:37:37.259 --> 00:37:39.279 whether the SNP is replicated

NOTE Confidence: 0.99458814

00:37:39.660 --> 00:37:40.319 for association

NOTE Confidence: 0.9165355

00:37:41.019 --> 00:37:42.380 with rate of dilation as

NOTE Confidence: 0.9165355

00:37:42.380 --> 00:37:43.180 well as looking at other

NOTE Confidence: 0.9165355

00:37:43.180 --> 00:37:44.184 candidate snips such such as

NOTE Confidence: 0.9165355

00:37:44.184 --> 00:37:44.924 some of those

NOTE Confidence: 0.9772694

00:37:45.305 --> 00:37:46.424 genes that were identified in

NOTE Confidence: 0.9772694

00:37:46.424 --> 00:37:46.924 GWAS.

NOTE Confidence: 0.70896137

00:37:48.265 --> 00:37:49.005 And so,

NOTE Confidence: 0.9340665

00:37:49.704 --> 00:37:50.825 transitioning a little bit here.

NOTE Confidence: 0.9340665

00:37:50.825 --> 00:37:52.265 So, we've recently done a

NOTE Confidence: 0.9340665

00:37:52.265 --> 00:37:53.464 study in patients who have

NOTE Confidence: 0.9340665

00:37:53.464 --> 00:37:54.904 Marfan syndrome in Loewe's Dietzen,

NOTE Confidence: 0.9340665

00:37:54.904 --> 00:37:56.424 which we've taken a frozen

NOTE Confidence: 0.9340665

00:37:56.424 --> 00:37:57.540 piece of tissue, split it,

NOTE Confidence: 0.9340665

00:37:57.620 --> 00:37:58.840 and done single cell transcriptome

NOTE Confidence: 0.9340665

00:37:58.900 --> 00:38:00.100 analysis using a fixed RNA

NOTE Confidence: 0.9340665

00:38:00.100 --> 00:38:00.600 profiling

NOTE Confidence: 0.8752356

00:38:01.060 --> 00:38:02.739 assay, and then also in

NOTE Confidence: 0.8752356

00:38:02.739 --> 00:38:04.840 parallel done, untargeted metabolomics,

NOTE Confidence: 0.9904081

00:38:05.620 --> 00:38:06.440 in those tissues.

NOTE Confidence: 0.8770872

00:38:07.140 --> 00:38:07.860 And this is kind of

NOTE Confidence: 0.8770872

00:38:07.860 --> 00:38:08.580 just gives you a map

NOTE Confidence: 0.8770872

00:38:08.580 --> 00:38:09.320 of the overall

NOTE Confidence: 0.56264114

00:38:09.860 --> 00:38:10.360 broad

NOTE Confidence: 0.6701177

00:38:17.685 --> 00:38:18.185 aortopathy,

NOTE Confidence: 0.9222928

00:38:18.805 --> 00:38:20.325 in terms of their proportions

NOTE Confidence: 0.9222928

00:38:20.325 --> 00:38:21.685 of small cell fibroblast may

NOTE Confidence: 0.9222928

00:38:21.685 --> 00:38:22.645 have been slightly different, but

NOTE Confidence: 0.9222928

00:38:22.645 --> 00:38:23.864 the remainder was similar.

NOTE Confidence: 0.9578949

00:38:24.640 --> 00:38:25.600 And then when we looked

NOTE Confidence: 0.9578949

00:38:25.600 --> 00:38:28.239 at the, untargeted metabolomics data,

NOTE Confidence: 0.9578949

00:38:28.239 --> 00:38:29.520 what we're observing in this,

NOTE Confidence: 0.9578949

00:38:29.760 --> 00:38:30.880 set of patients as well

NOTE Confidence: 0.9578949

00:38:30.880 --> 00:38:31.619 is increased,

NOTE Confidence: 0.9545296

00:38:32.239 --> 00:38:34.340 evidence for, oxidized glutathione

NOTE Confidence: 0.84326893

00:38:34.880 --> 00:38:36.180 relative to reduced glutathione.

NOTE Confidence: 0.9245379

00:38:36.480 --> 00:38:38.400 We also observed increased levels

NOTE Confidence: 0.9245379

00:38:38.400 --> 00:38:39.645 of long chain fatty acids.

NOTE Confidence: 0.9245379

00:38:39.885 --> 00:38:40.765 And then when we looked

NOTE Confidence: 0.9245379

00:38:40.765 --> 00:38:41.805 at the suitable data in

NOTE Confidence: 0.9245379

00:38:41.805 --> 00:38:42.465 the transcriptome,

NOTE Confidence: 0.91592556

00:38:42.925 --> 00:38:45.245 also identified decreased expression of

NOTE Confidence: 0.91592556

00:38:45.245 --> 00:38:46.445 genes that are very important

NOTE Confidence: 0.91592556

00:38:46.445 --> 00:38:48.065 for this, for the acylation

NOTE Confidence: 0.91592556

00:38:48.205 --> 00:38:49.725 of long chain fatty acids

NOTE Confidence: 0.91592556

00:38:49.725 --> 00:38:52.065 suggesting potentially a transcriptome

NOTE Confidence: 0.96421707

00:38:52.445 --> 00:38:54.140 metabolome connection as well as

NOTE Confidence: 0.96421707

00:38:54.140 --> 00:38:55.360 decreased levels of acylcarnitines,

NOTE Confidence: 0.92160493

00:38:56.540 --> 00:38:57.580 that were medium and long

NOTE Confidence: 0.92160493

00:38:57.580 --> 00:38:58.080 chain

NOTE Confidence: 0.9132178

00:38:58.620 --> 00:39:00.219 that, overall may indicate a

NOTE Confidence: 0.9132178

00:39:00.219 --> 00:39:00.719 decreased,

NOTE Confidence: 0.944991

00:39:01.340 --> 00:39:03.420 activation of beta oxidation in

NOTE Confidence: 0.944991

00:39:03.420 --> 00:39:05.200 in aortic aneurysm patients.

NOTE Confidence: 0.84127593

00:39:06.795 --> 00:39:07.535 And so,

NOTE Confidence: 0.96186507

00:39:08.395 --> 00:39:10.075 you know, thinking about our

NOTE Confidence: 0.96186507

00:39:10.075 --> 00:39:11.035 prior study in which we

NOTE Confidence: 0.96186507

00:39:11.035 --> 00:39:11.535 integrated,

NOTE Confidence: 0.9848085

00:39:11.915 --> 00:39:13.435 smooth muscle cell genome data

NOTE Confidence: 0.9848085

00:39:13.435 --> 00:39:15.114 with their transcriptome data from

NOTE Confidence: 0.9848085

00:39:15.114 --> 00:39:15.594 the,

NOTE Confidence: 0.9464508

00:39:16.155 --> 00:39:18.315 smooth muscle cells, we've expanded

NOTE Confidence: 0.9464508

00:39:18.315 --> 00:39:19.435 upon that and and by

NOTE Confidence: 0.9464508

00:39:19.435 --> 00:39:20.875 doing a larger cohort. And

NOTE Confidence: 0.9464508

00:39:20.875 --> 00:39:21.375 so,

NOTE Confidence: 0.9162465

00:39:21.890 --> 00:39:23.350 we're, we've done

NOTE Confidence: 0.9040654

00:39:23.969 --> 00:39:25.030 genome and transcriptome

NOTE Confidence: 0.9987427

00:39:25.410 --> 00:39:26.310 analysis for

NOTE Confidence: 0.94802976

00:39:26.610 --> 00:39:28.690 sixty three cases and fourteen

NOTE Confidence: 0.94802976

00:39:28.690 --> 00:39:29.190 controls

NOTE Confidence: 0.93899465

00:39:29.650 --> 00:39:30.770 using the same approach where

NOTE Confidence: 0.93899465

00:39:30.770 --> 00:39:31.890 we did whole genome sequencing

NOTE Confidence: 0.93899465

00:39:31.890 --> 00:39:32.850 for the patient and then

NOTE Confidence: 0.93899465

00:39:32.850 --> 00:39:34.370 mRNA sequencing of the smooth

NOTE Confidence: 0.93899465

00:39:34.370 --> 00:39:35.670 muscle cells that were extracted.

NOTE Confidence: 0.94518965

00:39:35.985 --> 00:39:36.885 And in this,

NOTE Confidence: 0.9868397

00:39:38.145 --> 00:39:39.765 study, we're hypothesizing

NOTE Confidence: 0.9897844

00:39:40.065 --> 00:39:42.165 that differences in allelic expression,

NOTE Confidence: 0.8044894

00:39:42.864 --> 00:39:43.364 between,

NOTE Confidence: 0.9589139

00:39:43.985 --> 00:39:45.585 cases and controls may be

NOTE Confidence: 0.9589139

00:39:45.585 --> 00:39:47.364 a clue to the, mechanisms

NOTE Confidence: 0.9589139

00:39:47.505 --> 00:39:49.045 of TA development and progression.

NOTE Confidence: 0.9080028

00:39:49.760 --> 00:39:51.280 And so the the approach

NOTE Confidence: 0.9080028

00:39:51.280 --> 00:39:52.239 here is we we called

NOTE Confidence: 0.9080028

00:39:52.239 --> 00:39:53.920 bio allelic SNPs using genome

NOTE Confidence: 0.9080028

00:39:53.920 --> 00:39:55.520 data. We did, we counted

NOTE Confidence: 0.9080028

00:39:55.520 --> 00:39:56.800 up the number of reads

NOTE Confidence: 0.9080028

00:39:56.800 --> 00:39:58.880 using a a GATK ASE

NOTE Confidence: 0.9080028

00:39:58.880 --> 00:40:00.640 recounter in the mRNA seek

NOTE Confidence: 0.9080028

00:40:00.640 --> 00:40:01.760 data, and then you compare

NOTE Confidence: 0.9080028

00:40:01.760 --> 00:40:04.000 those using we we performed

NOTE Confidence: 0.9080028

00:40:04.000 --> 00:40:05.655 an analysis of this differential

NOTE Confidence: 0.9080028

00:40:05.655 --> 00:40:07.035 allelic expression using,

NOTE Confidence: 0.99117666

00:40:07.415 --> 00:40:09.015 this this score. And then

NOTE Confidence: 0.99117666

00:40:09.015 --> 00:40:09.835 we also did

NOTE Confidence: 0.9603043

00:40:10.295 --> 00:40:11.975 a a differential gene expression

NOTE Confidence: 0.9603043

00:40:11.975 --> 00:40:13.355 analysis using ADJAR.

NOTE Confidence: 0.96949077

00:40:13.735 --> 00:40:15.255 And so the results of

NOTE Confidence: 0.96949077

00:40:15.255 --> 00:40:17.255 this differential allele specific expression

NOTE Confidence: 0.96949077

00:40:17.255 --> 00:40:18.695 analysis, these are,

NOTE Confidence: 0.9521657

00:40:19.760 --> 00:40:21.359 you know, recent recent results.

NOTE Confidence: 0.9521657

00:40:21.359 --> 00:40:22.480 So the the way that

NOTE Confidence: 0.9521657

00:40:22.480 --> 00:40:23.940 we are are measuring,

NOTE Confidence: 0.6797595

00:40:24.559 --> 00:40:25.780 differential allele

NOTE Confidence: 0.88094616

00:40:26.239 --> 00:40:27.300 specific expression,

NOTE Confidence: 0.93136275

00:40:27.839 --> 00:40:29.760 is this parameter in ASC

NOTE Confidence: 0.93136275

00:40:29.760 --> 00:40:31.680 score, which is really, testing

NOTE Confidence: 0.93136275

00:40:31.680 --> 00:40:32.900 the degree of disproportion

NOTE Confidence: 0.8734829

00:40:33.599 --> 00:40:35.995 between, the sick reads between

NOTE Confidence: 0.8734829

00:40:36.055 --> 00:40:36.555 alleles,

NOTE Confidence: 0.9942089

00:40:37.015 --> 00:40:38.135 and then taking that score

NOTE Confidence: 0.9942089

00:40:38.135 --> 00:40:39.355 and doing a case control

NOTE Confidence: 0.9942089

00:40:39.415 --> 00:40:39.915 comparison.

NOTE Confidence: 0.86671567

00:40:40.295 --> 00:40:41.815 And that's the top five

NOTE Confidence: 0.86671567

00:40:41.815 --> 00:40:43.114 most significant loci,

NOTE Confidence: 0.9741866

00:40:43.895 --> 00:40:45.094 are listed here in this

NOTE Confidence: 0.9741866

00:40:45.094 --> 00:40:45.594 table.

NOTE Confidence: 0.8184853

00:40:45.895 --> 00:40:46.395 And

NOTE Confidence: 0.9137561

00:40:47.140 --> 00:40:48.180 and of interest, you know,

NOTE Confidence: 0.9137561

00:40:48.180 --> 00:40:49.780 we we see second here

NOTE Confidence: 0.9137561

00:40:49.780 --> 00:40:51.060 is another gene that's important

NOTE Confidence: 0.9137561

00:40:51.060 --> 00:40:52.440 for CoQ biosynthesis,

NOTE Confidence: 0.9871378

00:40:53.460 --> 00:40:53.960 CoQ

NOTE Confidence: 0.78094226

00:40:54.660 --> 00:40:55.160 seven.

NOTE Confidence: 0.9543946

00:40:57.780 --> 00:40:58.980 And then, you know, thinking

NOTE Confidence: 0.9543946

00:40:58.980 --> 00:41:00.340 about how if we see

NOTE Confidence: 0.9543946

00:41:00.340 --> 00:41:02.665 differential allelic expression, what could

NOTE Confidence: 0.9543946

00:41:02.665 --> 00:41:03.405 be the functional

NOTE Confidence: 0.93265486

00:41:03.785 --> 00:41:04.765 effect of that?

NOTE Confidence: 0.9593032

00:41:05.145 --> 00:41:06.364 As a really high level,

NOTE Confidence: 0.9139885

00:41:06.665 --> 00:41:07.565 test, we,

NOTE Confidence: 0.99107695

00:41:08.344 --> 00:41:09.704 we look for overlap between

NOTE Confidence: 0.99107695

00:41:09.704 --> 00:41:11.464 genes that were differentially expressed

NOTE Confidence: 0.99107695

00:41:11.464 --> 00:41:13.085 in TAA compared with controls

NOTE Confidence: 0.99107695

00:41:13.305 --> 00:41:14.105 and those that were

NOTE Confidence: 0.9936288

00:41:14.744 --> 00:41:16.045 that had significant

NOTE Confidence: 0.9208968

00:41:16.505 --> 00:41:17.005 loci

NOTE Confidence: 0.88566744

00:41:17.520 --> 00:41:17.920 that can

NOTE Confidence: 0.94707006

00:41:18.719 --> 00:41:20.080 that contained a loci that

NOTE Confidence: 0.94707006

00:41:20.080 --> 00:41:22.180 was significantly different between TAA

NOTE Confidence: 0.94707006

00:41:22.400 --> 00:41:24.239 and and and controls. And

NOTE Confidence: 0.94707006

00:41:24.239 --> 00:41:24.880 what you can see here

NOTE Confidence: 0.94707006

00:41:24.880 --> 00:41:26.080 is there's overlap of a

NOTE Confidence: 0.94707006

00:41:26.080 --> 00:41:27.520 hundred sixty seven genes that

NOTE Confidence: 0.94707006

00:41:27.520 --> 00:41:30.100 were differentially expressed in TAA

NOTE Confidence: 0.94707006

00:41:30.320 --> 00:41:31.540 and also displayed

NOTE Confidence: 0.9740571

00:41:31.864 --> 00:41:33.224 at least one loci with

NOTE Confidence: 0.9740571

00:41:33.224 --> 00:41:35.085 differential allele specific expression.

NOTE Confidence: 0.9955578

00:41:36.184 --> 00:41:37.944 Considering around thirteen thousand genes

NOTE Confidence: 0.9955578

00:41:37.944 --> 00:41:38.605 were tested,

NOTE Confidence: 0.9493008

00:41:38.984 --> 00:41:40.605 that's a significant overlap.

NOTE Confidence: 0.93182623

00:41:41.145 --> 00:41:42.424 And and of interest as

NOTE Confidence: 0.93182623

00:41:42.424 --> 00:41:43.800 well, you know, amongst this

NOTE Confidence: 0.93182623

00:41:44.280 --> 00:41:46.040 overlapping group is is is

NOTE Confidence: 0.93182623

00:41:46.040 --> 00:41:47.480 CoQ a b as well

NOTE Confidence: 0.93182623

00:41:47.480 --> 00:41:48.760 as another, the,

NOTE Confidence: 0.89147997

00:41:49.480 --> 00:41:50.760 homolog of CoQ a b,

NOTE Confidence: 0.89147997

00:41:50.760 --> 00:41:51.660 CoQ a a.

NOTE Confidence: 0.95556706

00:41:52.760 --> 00:41:53.719 And when we looked at,

NOTE Confidence: 0.95556706

00:41:53.880 --> 00:41:55.080 these a hundred sixty seven

NOTE Confidence: 0.95556706

00:41:55.080 --> 00:41:55.960 genes in terms of the

NOTE Confidence: 0.95556706

00:41:55.960 --> 00:41:57.665 pathways, we see that amongst

NOTE Confidence: 0.95556706

00:41:57.665 --> 00:41:59.105 those that have differential allele

NOTE Confidence: 0.95556706

00:41:59.105 --> 00:42:00.085 specific expression

NOTE Confidence: 0.9635949

00:42:00.465 --> 00:42:02.565 and increased gene expression levels,

NOTE Confidence: 0.98281956

00:42:03.025 --> 00:42:04.325 actin filament binding,

NOTE Confidence: 0.99131507

00:42:04.785 --> 00:42:06.565 was enriched amongst those genes,

NOTE Confidence: 0.99131507

00:42:06.785 --> 00:42:07.285 cytoskeletal

NOTE Confidence: 0.95311475

00:42:07.585 --> 00:42:09.025 binding. And amongst those that

NOTE Confidence: 0.95311475

00:42:09.025 --> 00:42:10.625 had decreased expression as well

NOTE Confidence: 0.95311475

00:42:10.625 --> 00:42:12.600 as, allele specific differential allele

NOTE Confidence: 0.95311475

00:42:12.680 --> 00:42:13.820 specific expression between

NOTE Confidence: 0.9037535

00:42:14.120 --> 00:42:15.560 cases and controls. We see,

NOTE Confidence: 0.9037535

00:42:15.800 --> 00:42:17.100 genes important for oxidoreductase

NOTE Confidence: 0.99622595

00:42:17.640 --> 00:42:18.140 activity,

NOTE Confidence: 0.88549024

00:42:19.480 --> 00:42:21.260 alcohol metabolic process, and isoprenoid

NOTE Confidence: 0.88549024

00:42:21.480 --> 00:42:22.700 metabolic process.

NOTE Confidence: 0.8471627

00:42:23.320 --> 00:42:24.140 And so,

NOTE Confidence: 0.97264063

00:42:25.175 --> 00:42:26.295 wanted to show the data

NOTE Confidence: 0.97264063

00:42:26.295 --> 00:42:28.055 specifically for the CoQAB. So,

NOTE Confidence: 0.95844513

00:42:28.695 --> 00:42:29.734 so here we see, as

NOTE Confidence: 0.95844513

00:42:29.734 --> 00:42:30.775 I mentioned, this is a

NOTE Confidence: 0.95844513

00:42:30.775 --> 00:42:32.375 larger subset of patients, seventy

NOTE Confidence: 0.95844513

00:42:32.375 --> 00:42:33.575 seven patients in which we

NOTE Confidence: 0.95844513

00:42:33.575 --> 00:42:35.195 see decreased expression of CoQAB

NOTE Confidence: 0.95844513

00:42:35.335 --> 00:42:37.114 and TAA smooth muscle cells.

NOTE Confidence: 0.9469966

00:42:37.734 --> 00:42:39.030 And and it was interesting

NOTE Confidence: 0.9469966

00:42:39.110 --> 00:42:40.310 because it was this the

NOTE Confidence: 0.9469966

00:42:40.310 --> 00:42:41.370 specific SNP,

NOTE Confidence: 0.985919

00:42:41.989 --> 00:42:43.350 that we identified as a

NOTE Confidence: 0.985919

00:42:43.350 --> 00:42:44.250 as a candidate,

NOTE Confidence: 0.9985362

00:42:44.630 --> 00:42:45.690 genetic modifier

NOTE Confidence: 0.95960045

00:42:45.989 --> 00:42:47.450 of the progression of disease

NOTE Confidence: 0.95960045

00:42:47.590 --> 00:42:48.710 that also that showed the

NOTE Confidence: 0.95960045

00:42:48.710 --> 00:42:49.989 allelic imbalance. And you can

NOTE Confidence: 0.95960045

00:42:49.989 --> 00:42:51.270 see here that, the fraction

NOTE Confidence: 0.95960045

00:42:51.270 --> 00:42:52.310 of reads with the alternative

NOTE Confidence: 0.95960045

00:42:52.310 --> 00:42:53.864 allele was higher in cases

NOTE Confidence: 0.95960045

00:42:53.864 --> 00:42:55.485 compared compared with controls.

NOTE Confidence: 0.94675446

00:42:55.864 --> 00:42:57.705 So potentially another, piece of

NOTE Confidence: 0.94675446

00:42:57.705 --> 00:42:58.985 evidence and try to trying

NOTE Confidence: 0.94675446

00:42:58.985 --> 00:43:00.265 to understand what is the

NOTE Confidence: 0.94675446

00:43:00.265 --> 00:43:02.025 mechanism by which a common

NOTE Confidence: 0.94675446

00:43:02.025 --> 00:43:02.525 SNP,

NOTE Confidence: 0.99217117

00:43:02.825 --> 00:43:05.145 could lead to, to, contribute

NOTE Confidence: 0.99217117

00:43:05.145 --> 00:43:06.285 to the disease pathogenesis.

NOTE Confidence: 0.98598725

00:43:07.320 --> 00:43:08.920 So there's limitations to to

NOTE Confidence: 0.98598725

00:43:08.920 --> 00:43:10.520 these data. It's it's cultured

NOTE Confidence: 0.98598725

00:43:10.520 --> 00:43:11.020 cells.

NOTE Confidence: 0.9448854

00:43:11.640 --> 00:43:13.739 It's, short read genome sequencing.

NOTE Confidence: 0.89748764

00:43:14.200 --> 00:43:15.880 So, the ability to phase

NOTE Confidence: 0.89748764

00:43:15.880 --> 00:43:17.880 variance is is challenging, if

NOTE Confidence: 0.89748764

00:43:17.880 --> 00:43:18.380 not

NOTE Confidence: 0.8317109

00:43:19.815 --> 00:43:20.635 if not impossible.

NOTE Confidence: 0.9706829

00:43:20.935 --> 00:43:21.655 And then we did short

NOTE Confidence: 0.9706829

00:43:21.655 --> 00:43:22.795 read mRNA sequencing.

NOTE Confidence: 0.9577882

00:43:23.895 --> 00:43:25.415 And so a better approach

NOTE Confidence: 0.9577882

00:43:25.415 --> 00:43:26.775 when it comes to phasing

NOTE Confidence: 0.9577882

00:43:26.775 --> 00:43:28.455 and allelic expression analysis would

NOTE Confidence: 0.9577882

00:43:28.455 --> 00:43:30.055 be long read. So, we

NOTE Confidence: 0.9577882

00:43:30.055 --> 00:43:31.015 are doing a study in

NOTE Confidence: 0.9577882

00:43:31.015 --> 00:43:31.815 which we're looking at the

NOTE Confidence: 0.9577882

00:43:31.815 --> 00:43:32.315 tissue,

NOTE Confidence: 0.9852011

00:43:32.855 --> 00:43:33.755 frozen tissue,

NOTE Confidence: 0.88359404

00:43:34.660 --> 00:43:36.020 extracting DNA, and performing,

NOTE Confidence: 0.9424756

00:43:36.980 --> 00:43:38.260 a long read whole genome

NOTE Confidence: 0.9424756

00:43:38.260 --> 00:43:40.520 sequencing using Oxford Nanopore technology,

NOTE Confidence: 0.98058623

00:43:41.219 --> 00:43:42.739 which gives you also base,

NOTE Confidence: 0.98058623

00:43:43.060 --> 00:43:44.520 base modification data,

NOTE Confidence: 0.94802684

00:43:44.820 --> 00:43:46.180 and integrating that with the

NOTE Confidence: 0.94802684

00:43:46.180 --> 00:43:48.275 short read mRNA sequencing data.

NOTE Confidence: 0.94802684

00:43:48.415 --> 00:43:49.694 And we have collected enough

NOTE Confidence: 0.94802684

00:43:49.694 --> 00:43:50.895 patients where about a hun

NOTE Confidence: 0.94802684

00:43:51.055 --> 00:43:52.575 a hundred patients are are

NOTE Confidence: 0.94802684

00:43:52.575 --> 00:43:54.174 done now for this. And

NOTE Confidence: 0.94802684

00:43:54.174 --> 00:43:55.135 so we're gonna use this

NOTE Confidence: 0.94802684

00:43:55.135 --> 00:43:56.755 as another way to investigate

NOTE Confidence: 0.94802684

00:43:56.815 --> 00:43:58.655 differential allele specific expression as

NOTE Confidence: 0.94802684

00:43:58.655 --> 00:43:59.714 well as other possibilities.

NOTE Confidence: 0.9987277

00:44:00.094 --> 00:44:00.594 We're

NOTE Confidence: 0.92397475

00:44:01.320 --> 00:44:02.860 combining, those data,

NOTE Confidence: 0.87108916

00:44:03.400 --> 00:44:03.900 and,

NOTE Confidence: 0.9928779

00:44:04.760 --> 00:44:06.280 and taking you know, trying

NOTE Confidence: 0.9928779

00:44:06.280 --> 00:44:08.360 to prioritize what may be

NOTE Confidence: 0.9928779

00:44:08.360 --> 00:44:09.820 observed in the human,

NOTE Confidence: 0.8916089

00:44:10.280 --> 00:44:10.780 endogenous

NOTE Confidence: 0.99912316

00:44:11.080 --> 00:44:11.580 setting

NOTE Confidence: 0.9556114

00:44:11.880 --> 00:44:14.040 by, using a massively parallel

NOTE Confidence: 0.9556114

00:44:14.040 --> 00:44:15.880 reporter assays that are going

NOTE Confidence: 0.9556114

00:44:15.880 --> 00:44:17.505 to be determining in smooth

NOTE Confidence: 0.9556114

00:44:17.505 --> 00:44:18.325 muscle cells,

NOTE Confidence: 0.99859643

00:44:18.625 --> 00:44:19.525 what's the transcriptional

NOTE Confidence: 0.9524126

00:44:19.825 --> 00:44:21.025 effect of variants that are

NOTE Confidence: 0.9524126

00:44:21.025 --> 00:44:23.184 look localizing in, three prime

NOTE Confidence: 0.9524126

00:44:23.184 --> 00:44:23.684 UTRs

NOTE Confidence: 0.85781145

00:44:24.145 --> 00:44:25.444 and putative noncoding

NOTE Confidence: 0.9610597

00:44:25.825 --> 00:44:27.105 elements as a way to

NOTE Confidence: 0.9610597

00:44:27.105 --> 00:44:27.925 begin to,

NOTE Confidence: 0.9396357

00:44:28.305 --> 00:44:29.744 sort through what whole genome

NOTE Confidence: 0.9396357

00:44:29.744 --> 00:44:30.640 data looks like and how

NOTE Confidence: 0.9396357

00:44:30.640 --> 00:44:32.000 that integrates with RNA Seq

NOTE Confidence: 0.9396357

00:44:32.000 --> 00:44:32.500 data.

NOTE Confidence: 0.89197135

00:44:33.040 --> 00:44:34.180 Okay. So,

NOTE Confidence: 0.9898062

00:44:36.239 --> 00:44:37.920 very much switching gears from

NOTE Confidence: 0.9898062

00:44:37.920 --> 00:44:39.280 from the from the tissue

NOTE Confidence: 0.9898062

00:44:39.280 --> 00:44:39.780 studies,

NOTE Confidence: 0.99662864

00:44:40.480 --> 00:44:41.380 but connected

NOTE Confidence: 0.96608746

00:44:41.760 --> 00:44:43.040 clinically and on a research

NOTE Confidence: 0.96608746

00:44:43.040 --> 00:44:44.160 basis is I wanted to

NOTE Confidence: 0.96608746

00:44:44.160 --> 00:44:45.405 talk about a technique that

NOTE Confidence: 0.96608746

00:44:45.405 --> 00:44:47.005 we've developed in collaboration with

NOTE Confidence: 0.96608746

00:44:47.005 --> 00:44:47.505 engineers

NOTE Confidence: 0.9381302

00:44:48.045 --> 00:44:49.105 at Purdue University

NOTE Confidence: 0.9663434

00:44:49.885 --> 00:44:51.005 to try to improve our

NOTE Confidence: 0.9663434

00:44:51.005 --> 00:44:51.505 ability

NOTE Confidence: 0.9959135

00:44:51.885 --> 00:44:53.265 to phenotype patients

NOTE Confidence: 0.9518179

00:44:53.725 --> 00:44:54.705 using transthoracic

NOTE Confidence: 0.9075661

00:44:55.005 --> 00:44:55.505 echocardiography,

NOTE Confidence: 0.9358741

00:44:56.765 --> 00:44:59.025 including more accurate measurements, reproducible

NOTE Confidence: 0.9516338

00:44:59.565 --> 00:45:00.060 measurements,

NOTE Confidence: 0.9623447

00:45:01.340 --> 00:45:03.020 greater throughput, as well as

NOTE Confidence: 0.9623447

00:45:03.020 --> 00:45:03.520 extracting

NOTE Confidence: 0.95943856

00:45:03.820 --> 00:45:05.500 more functional data than what

NOTE Confidence: 0.95943856

00:45:05.500 --> 00:45:06.719 is the standard approach.

NOTE Confidence: 0.841415

00:45:07.739 --> 00:45:09.260 Our standard approach, as we

NOTE Confidence: 0.841415

00:45:09.260 --> 00:45:10.320 know, when it comes to

NOTE Confidence: 0.841415

00:45:10.460 --> 00:45:12.060 aortic characterization would be to

NOTE Confidence: 0.841415

00:45:12.060 --> 00:45:13.360 make measurements at the annulus,

NOTE Confidence: 0.841415

00:45:13.575 --> 00:45:14.535 aortic group, the San Diego

NOTE Confidence: 0.841415

00:45:14.535 --> 00:45:15.675 Junction ascending aorta.

NOTE Confidence: 0.97189844

00:45:16.295 --> 00:45:17.815 Calculate z scores in kids,

NOTE Confidence: 0.97189844

00:45:17.815 --> 00:45:19.015 and there's your phenotype. So

NOTE Confidence: 0.97189844

00:45:19.015 --> 00:45:19.734 it's it's kind of,

NOTE Confidence: 0.89816624

00:45:20.695 --> 00:45:21.195 woefully,

NOTE Confidence: 0.9544826

00:45:21.815 --> 00:45:23.335 simple, I would say, when

NOTE Confidence: 0.9544826

00:45:23.335 --> 00:45:24.055 it comes to how we're

NOTE Confidence: 0.9544826

00:45:24.055 --> 00:45:26.214 classifying or or characterizing our

NOTE Confidence: 0.9544826

00:45:26.214 --> 00:45:27.415 our patients' disease. So that

NOTE Confidence: 0.9544826

00:45:27.415 --> 00:45:28.474 was kind of a motivation

NOTE Confidence: 0.9544826

00:45:28.535 --> 00:45:30.070 for trying to do this.

NOTE Confidence: 0.9544826

00:45:30.070 --> 00:45:31.390 So, I think what you

NOTE Confidence: 0.9544826

00:45:31.390 --> 00:45:32.150 can see here, right, is

NOTE Confidence: 0.9544826

00:45:32.190 --> 00:45:33.469 so, this is a b

NOTE Confidence: 0.9544826

00:45:33.469 --> 00:45:34.910 mode. Right? And we've just

NOTE Confidence: 0.9544826

00:45:34.910 --> 00:45:36.270 put a plane here, you

NOTE Confidence: 0.9544826

00:45:36.270 --> 00:45:37.469 know, to highlight the fact

NOTE Confidence: 0.9544826

00:45:37.469 --> 00:45:38.690 that there's tons of translation,

NOTE Confidence: 0.9544826

00:45:38.750 --> 00:45:39.790 right, of the aortic root

NOTE Confidence: 0.9544826

00:45:39.790 --> 00:45:41.230 through cardiac cycles. When would

NOTE Confidence: 0.9544826

00:45:41.230 --> 00:45:42.425 you make the measurement? Know,

NOTE Confidence: 0.9544826

00:45:42.425 --> 00:45:43.465 what borders are you using?

NOTE Confidence: 0.9544826

00:45:43.465 --> 00:45:44.585 What what's at what plane

NOTE Confidence: 0.9544826

00:45:44.585 --> 00:45:45.785 are you measuring? All these

NOTE Confidence: 0.9544826

00:45:45.785 --> 00:45:46.605 things are confounding

NOTE Confidence: 0.9444615

00:45:46.984 --> 00:45:48.105 factors when it comes to

NOTE Confidence: 0.9444615

00:45:48.105 --> 00:45:49.484 research and clinical care.

NOTE Confidence: 0.99400735

00:45:50.105 --> 00:45:51.465 And and so we've developed

NOTE Confidence: 0.99400735

00:45:51.465 --> 00:45:53.224 this algorithm that's designed to

NOTE Confidence: 0.99400735

00:45:53.224 --> 00:45:54.285 track the translation

NOTE Confidence: 0.9874901

00:45:54.665 --> 00:45:56.289 of the aortic root. So

NOTE Confidence: 0.9874901

00:45:56.289 --> 00:45:58.289 it's tracking, the translation in

NOTE Confidence: 0.9874901

00:45:58.289 --> 00:45:58.950 the x,

NOTE Confidence: 0.96296805

00:45:59.250 --> 00:46:01.109 direction, y direction, and rotation,

NOTE Confidence: 0.9778479

00:46:01.569 --> 00:46:02.469 in the theta.

NOTE Confidence: 0.9607092

00:46:05.730 --> 00:46:07.170 Okay. And you can see

NOTE Confidence: 0.9607092

00:46:07.170 --> 00:46:07.969 here, this is a this

NOTE Confidence: 0.9607092

00:46:07.969 --> 00:46:09.329 is a representation of that

NOTE Confidence: 0.9607092

00:46:09.329 --> 00:46:09.829 data,

NOTE Confidence: 0.95231134

00:46:10.185 --> 00:46:11.385 for this sample I mean,

NOTE Confidence: 0.95231134

00:46:11.385 --> 00:46:12.844 for this, for this series.

NOTE Confidence: 0.97859687

00:46:13.625 --> 00:46:14.665 And then what we get

NOTE Confidence: 0.97859687

00:46:14.665 --> 00:46:14.905 out,

NOTE Confidence: 0.9621042

00:46:15.705 --> 00:46:17.965 after the, algorithm runs and

NOTE Confidence: 0.9621042

00:46:18.025 --> 00:46:18.925 when this runs

NOTE Confidence: 0.9648412

00:46:22.119 --> 00:46:23.480 Okay. Is that the the

NOTE Confidence: 0.9648412

00:46:23.480 --> 00:46:24.680 algorithm, what it's doing is

NOTE Confidence: 0.9648412

00:46:24.680 --> 00:46:26.119 is using these parameters to

NOTE Confidence: 0.9648412

00:46:26.119 --> 00:46:28.280 stabilize the aortic root, within

NOTE Confidence: 0.9648412

00:46:28.280 --> 00:46:29.400 the image, and then you

NOTE Confidence: 0.9648412

00:46:29.400 --> 00:46:30.440 can take these data that's

NOTE Confidence: 0.9648412

00:46:30.440 --> 00:46:32.140 now stabilized and extract,

NOTE Confidence: 0.9998596

00:46:32.760 --> 00:46:33.820 diameter information

NOTE Confidence: 0.99486214

00:46:34.215 --> 00:46:35.915 that is in a consistent

NOTE Confidence: 0.99486214

00:46:35.975 --> 00:46:36.475 plane,

NOTE Confidence: 0.94840753

00:46:37.015 --> 00:46:38.375 through the aortic root. And

NOTE Confidence: 0.94840753

00:46:38.375 --> 00:46:39.255 you can see here we're

NOTE Confidence: 0.94840753

00:46:39.255 --> 00:46:40.215 starting to detect,

NOTE Confidence: 0.9555201

00:46:40.535 --> 00:46:41.835 you know, kind of subtle

NOTE Confidence: 0.9555201

00:46:41.895 --> 00:46:43.655 deflections in the aortic root

NOTE Confidence: 0.9555201

00:46:43.655 --> 00:46:44.155 diameter,

NOTE Confidence: 0.99896073

00:46:44.535 --> 00:46:45.735 through the course of cardiac

NOTE Confidence: 0.99896073

00:46:45.735 --> 00:46:46.235 cycles.

NOTE Confidence: 0.9593501

00:46:46.710 --> 00:46:47.210 And

NOTE Confidence: 0.96011573

00:46:47.589 --> 00:46:49.030 the way this works, just

NOTE Confidence: 0.96011573

00:46:49.030 --> 00:46:49.770 just briefly,

NOTE Confidence: 0.9486908

00:46:50.070 --> 00:46:51.270 is that we we take

NOTE Confidence: 0.9486908

00:46:51.270 --> 00:46:53.109 a, a DICOM file, convert

NOTE Confidence: 0.9486908

00:46:53.109 --> 00:46:54.330 it to a MATLAB,

NOTE Confidence: 0.8447594

00:46:55.030 --> 00:46:55.530 file,

NOTE Confidence: 0.995734

00:46:55.910 --> 00:46:57.270 and then there's user input

NOTE Confidence: 0.995734

00:46:57.270 --> 00:46:58.070 when it comes to this.

NOTE Confidence: 0.995734

00:46:58.070 --> 00:46:59.530 So a user will will

NOTE Confidence: 0.9511329

00:46:59.885 --> 00:47:00.844 right will pull up the

NOTE Confidence: 0.9511329

00:47:00.844 --> 00:47:02.605 program, define the the plane

NOTE Confidence: 0.9511329

00:47:02.605 --> 00:47:03.724 of the annulus, define the

NOTE Confidence: 0.9511329

00:47:03.724 --> 00:47:05.344 plane of the sinotubular junction.

NOTE Confidence: 0.9511329

00:47:05.565 --> 00:47:07.165 The algorithm will then rotate,

NOTE Confidence: 0.9511329

00:47:07.325 --> 00:47:08.444 the aorta so that we're

NOTE Confidence: 0.9511329

00:47:08.444 --> 00:47:10.605 perpendicular to the longitudinal axis

NOTE Confidence: 0.9511329

00:47:10.605 --> 00:47:11.425 of axis,

NOTE Confidence: 0.99785054

00:47:11.964 --> 00:47:13.405 and then generate these contours

NOTE Confidence: 0.99785054

00:47:13.405 --> 00:47:14.444 that can be fine tuned

NOTE Confidence: 0.99785054

00:47:14.444 --> 00:47:15.150 by the user.

NOTE Confidence: 0.9335288

00:47:16.989 --> 00:47:18.930 From there, it's a, iterative

NOTE Confidence: 0.9335288

00:47:18.989 --> 00:47:20.849 frame by frame difference minimization

NOTE Confidence: 0.9674084

00:47:21.230 --> 00:47:22.750 algorithm that will be tracking

NOTE Confidence: 0.9674084

00:47:22.750 --> 00:47:23.890 the aortic translation,

NOTE Confidence: 0.97580487

00:47:24.349 --> 00:47:25.869 and adjusting the parameters of

NOTE Confidence: 0.97580487

00:47:25.869 --> 00:47:27.569 x, y, and theta.

NOTE Confidence: 0.9550725

00:47:28.835 --> 00:47:29.875 And and one of the

NOTE Confidence: 0.9550725

00:47:29.875 --> 00:47:31.474 outputs from this is, aortic

NOTE Confidence: 0.9550725

00:47:31.474 --> 00:47:33.474 diameter time course tracing through

NOTE Confidence: 0.9550725

00:47:33.474 --> 00:47:34.454 cardiac cycles.

NOTE Confidence: 0.989538

00:47:34.994 --> 00:47:36.295 And so what we've observed,

NOTE Confidence: 0.9947531

00:47:36.755 --> 00:47:37.494 is bimodal

NOTE Confidence: 0.9574344

00:47:37.795 --> 00:47:39.494 behavior. So in systole,

NOTE Confidence: 0.9986355

00:47:40.035 --> 00:47:40.535 aortic

NOTE Confidence: 0.97898746

00:47:41.020 --> 00:47:42.480 root diameter will increase.

NOTE Confidence: 0.94987696

00:47:42.860 --> 00:47:44.460 In end systole, there's a

NOTE Confidence: 0.94987696

00:47:44.460 --> 00:47:45.739 a a recoil. And then

NOTE Confidence: 0.94987696

00:47:45.739 --> 00:47:46.400 in diastole,

NOTE Confidence: 0.97079647

00:47:47.100 --> 00:47:48.700 a re expansion. And then,

NOTE Confidence: 0.97079647

00:47:48.700 --> 00:47:49.660 you know, through the course

NOTE Confidence: 0.97079647

00:47:49.660 --> 00:47:50.800 of diastole then,

NOTE Confidence: 0.9864342

00:47:51.580 --> 00:47:53.340 further contraction or or or

NOTE Confidence: 0.9864342

00:47:53.340 --> 00:47:53.840 recoil

NOTE Confidence: 0.826581

00:47:54.220 --> 00:47:54.960 of the diameter.

NOTE Confidence: 0.95984036

00:47:56.135 --> 00:47:57.734 So from these curves, we're

NOTE Confidence: 0.95984036

00:47:57.734 --> 00:47:59.175 able to extract the maximum

NOTE Confidence: 0.95984036

00:47:59.175 --> 00:48:00.155 systolic diameter,

NOTE Confidence: 0.9983902

00:48:01.815 --> 00:48:02.315 quantitatively

NOTE Confidence: 0.84973574

00:48:02.695 --> 00:48:04.075 and unbiased way,

NOTE Confidence: 0.9775488

00:48:04.855 --> 00:48:06.474 the end diastolic diameter,

NOTE Confidence: 0.9156541

00:48:07.255 --> 00:48:07.734 which,

NOTE Confidence: 0.99375075

00:48:08.055 --> 00:48:09.850 is notoriously tricky, I think,

NOTE Confidence: 0.99375075

00:48:09.850 --> 00:48:11.469 to to to to capture.

NOTE Confidence: 0.722088

00:48:13.130 --> 00:48:13.850 And then,

NOTE Confidence: 0.95855546

00:48:15.530 --> 00:48:16.330 and so when it comes

NOTE Confidence: 0.95855546

00:48:16.330 --> 00:48:17.950 to diameter measurements, we

NOTE Confidence: 0.93770766

00:48:18.250 --> 00:48:18.750 we

NOTE Confidence: 0.957214

00:48:19.130 --> 00:48:20.810 ran the algorithm and then,

NOTE Confidence: 0.957214

00:48:21.050 --> 00:48:22.030 and then validated,

NOTE Confidence: 0.98363733

00:48:22.410 --> 00:48:24.915 compared those to manual measurements,

NOTE Confidence: 0.958482

00:48:25.694 --> 00:48:26.915 and and saw a good

NOTE Confidence: 0.958482

00:48:26.974 --> 00:48:27.474 agreement,

NOTE Confidence: 0.93767625

00:48:27.855 --> 00:48:29.135 maybe a slight bias for

NOTE Confidence: 0.93767625

00:48:29.135 --> 00:48:30.895 higher diameter measurements with the

NOTE Confidence: 0.93767625

00:48:30.895 --> 00:48:32.734 algorithm compared to to the

NOTE Confidence: 0.93767625

00:48:32.734 --> 00:48:33.934 manual, but overall, a good

NOTE Confidence: 0.93767625

00:48:33.934 --> 00:48:35.310 interclass correlation coefficient,

NOTE Confidence: 0.92754304

00:48:36.270 --> 00:48:38.270 between the algorithm's output and

NOTE Confidence: 0.92754304

00:48:38.270 --> 00:48:39.250 the manual measurement.

NOTE Confidence: 0.92717224

00:48:40.430 --> 00:48:41.469 And then also from these

NOTE Confidence: 0.92717224

00:48:41.469 --> 00:48:42.910 data, which I'll show, we

NOTE Confidence: 0.92717224

00:48:42.989 --> 00:48:44.270 with our you know, with

NOTE Confidence: 0.92717224

00:48:44.270 --> 00:48:45.950 the availability of a maximum

NOTE Confidence: 0.92717224

00:48:45.950 --> 00:48:47.870 systolic diameter and a minimum

NOTE Confidence: 0.92717224

00:48:47.870 --> 00:48:49.785 and diastolic diameter, able to

NOTE Confidence: 0.7051121

00:48:50.085 --> 00:48:50.585 calculate,

NOTE Confidence: 0.96279794

00:48:51.364 --> 00:48:51.864 biomechanical

NOTE Confidence: 0.9957654

00:48:52.165 --> 00:48:53.305 properties as well

NOTE Confidence: 0.8437064

00:48:53.605 --> 00:48:55.364 using this. So, you know,

NOTE Confidence: 0.8437064

00:48:55.364 --> 00:48:56.885 we looked at these patients

NOTE Confidence: 0.8437064

00:48:56.885 --> 00:48:58.645 twenty controls, fifteen Marfan Syndrome,

NOTE Confidence: 0.8437064

00:48:58.645 --> 00:49:00.025 aged ten to fifteen years.

NOTE Confidence: 0.9621124

00:49:00.645 --> 00:49:02.025 As expected, the diameters

NOTE Confidence: 0.979408

00:49:02.325 --> 00:49:03.750 extracted by the algorithm were

NOTE Confidence: 0.979408

00:49:04.310 --> 00:49:04.810 larger,

NOTE Confidence: 0.9729096

00:49:05.110 --> 00:49:06.630 in Marfan syndrome compared to

NOTE Confidence: 0.9729096

00:49:06.630 --> 00:49:07.130 controls.

NOTE Confidence: 0.9719297

00:49:07.670 --> 00:49:08.570 And then interestingly,

NOTE Confidence: 0.9275789

00:49:09.270 --> 00:49:10.650 when we use the delta,

NOTE Confidence: 0.92727077

00:49:12.230 --> 00:49:14.170 in diastolic to maximum systolic

NOTE Confidence: 0.92727077

00:49:14.230 --> 00:49:16.325 data, we're seeing increased stiffness

NOTE Confidence: 0.92727077

00:49:16.325 --> 00:49:17.605 of the of the aortic

NOTE Confidence: 0.92727077

00:49:17.605 --> 00:49:18.505 root in Marfan,

NOTE Confidence: 0.85204095

00:49:18.885 --> 00:49:20.585 decreased strain, and decreased,

NOTE Confidence: 0.9106314

00:49:20.885 --> 00:49:21.385 distensibility.

NOTE Confidence: 0.9783166

00:49:21.765 --> 00:49:23.125 So so, you know, as

NOTE Confidence: 0.9783166

00:49:23.125 --> 00:49:24.404 a as a pilot study

NOTE Confidence: 0.9783166

00:49:24.404 --> 00:49:25.444 to say, we might be

NOTE Confidence: 0.9783166

00:49:25.444 --> 00:49:26.424 able to extract

NOTE Confidence: 0.93825006

00:49:26.724 --> 00:49:29.385 more comprehensive biomechanical properties using

NOTE Confidence: 0.93825006

00:49:29.444 --> 00:49:30.904 this tracking algorithm.

NOTE Confidence: 0.9720799

00:49:33.050 --> 00:49:34.250 And then also, you know,

NOTE Confidence: 0.9720799

00:49:34.250 --> 00:49:35.850 we've thought about how else

NOTE Confidence: 0.9720799

00:49:35.850 --> 00:49:37.210 we may be what other

NOTE Confidence: 0.9720799

00:49:37.210 --> 00:49:38.810 data may be useful here.

NOTE Confidence: 0.9720799

00:49:38.810 --> 00:49:39.310 So,

NOTE Confidence: 0.9946164

00:49:39.610 --> 00:49:40.410 you know, we see a

NOTE Confidence: 0.9946164

00:49:40.410 --> 00:49:41.950 rate of systolic expansion,

NOTE Confidence: 0.96371734

00:49:42.410 --> 00:49:43.950 a rate of systolic recoil,

NOTE Confidence: 0.96371734

00:49:44.114 --> 00:49:45.015 a rate of,

NOTE Confidence: 0.96337855

00:49:45.715 --> 00:49:47.395 diastolic expansion, and the rate

NOTE Confidence: 0.96337855

00:49:47.395 --> 00:49:48.994 of diastolic recoil. And we

NOTE Confidence: 0.96337855

00:49:48.994 --> 00:49:50.435 compare those between the Marfan

NOTE Confidence: 0.96337855

00:49:50.435 --> 00:49:50.935 syndrome,

NOTE Confidence: 0.8849376

00:49:51.555 --> 00:49:53.155 cases and the controls. And

NOTE Confidence: 0.8849376

00:49:53.155 --> 00:49:54.855 we're seeing a slower

NOTE Confidence: 0.95654607

00:49:55.235 --> 00:49:56.295 rate of recoil,

NOTE Confidence: 0.90892714

00:49:57.170 --> 00:49:58.210 at the end of in

NOTE Confidence: 0.90892714

00:49:58.210 --> 00:49:59.330 in the end systole in

NOTE Confidence: 0.90892714

00:49:59.330 --> 00:50:00.530 patients with a Marfan syndrome

NOTE Confidence: 0.90892714

00:50:00.530 --> 00:50:01.730 compared to controls. And, you

NOTE Confidence: 0.90892714

00:50:01.730 --> 00:50:02.630 know, trying to,

NOTE Confidence: 0.97576374

00:50:04.610 --> 00:50:05.730 you know, kind of think

NOTE Confidence: 0.97576374

00:50:05.730 --> 00:50:07.410 about how that may relate

NOTE Confidence: 0.97576374

00:50:07.410 --> 00:50:08.230 to intrinsic,

NOTE Confidence: 0.94726455

00:50:08.690 --> 00:50:10.130 elastic fiber differences in a

NOTE Confidence: 0.94726455

00:50:10.130 --> 00:50:11.670 Marfan syndrome, for example.

NOTE Confidence: 0.95402664

00:50:13.385 --> 00:50:14.825 And so, you know, with

NOTE Confidence: 0.95402664

00:50:14.825 --> 00:50:16.265 this algorithm, we're, you know,

NOTE Confidence: 0.95402664

00:50:16.265 --> 00:50:18.025 seeking to establish normative values

NOTE Confidence: 0.95402664

00:50:18.025 --> 00:50:18.685 for these,

NOTE Confidence: 0.9470324

00:50:19.224 --> 00:50:20.984 metrics, which are currently not

NOTE Confidence: 0.9470324

00:50:20.984 --> 00:50:21.724 not available,

NOTE Confidence: 0.97721016

00:50:22.185 --> 00:50:23.625 across age ranges. We'll do

NOTE Confidence: 0.97721016

00:50:23.625 --> 00:50:25.244 more case control comparisons,

NOTE Confidence: 0.90735996

00:50:26.000 --> 00:50:27.359 you know, thinking about how

NOTE Confidence: 0.90735996

00:50:27.359 --> 00:50:28.480 we predict risk. You know,

NOTE Confidence: 0.90735996

00:50:28.480 --> 00:50:29.280 is there a way to

NOTE Confidence: 0.90735996

00:50:29.280 --> 00:50:30.079 identify subtle biomarker

NOTE Confidence: 0.87168264

00:50:31.920 --> 00:50:33.780 maybe subtle, maybe just unassertainable

NOTE Confidence: 0.8969509

00:50:34.239 --> 00:50:35.460 previously biomechanical

NOTE Confidence: 0.954017

00:50:35.839 --> 00:50:37.200 properties that could be predictive

NOTE Confidence: 0.954017

00:50:37.200 --> 00:50:38.079 in a patient who has

NOTE Confidence: 0.954017

00:50:38.079 --> 00:50:39.599 a an aortic root diameter

NOTE Confidence: 0.954017

00:50:39.599 --> 00:50:41.415 of future progression, for example.

NOTE Confidence: 0.98164517

00:50:42.455 --> 00:50:43.895 Probably, this will improve our

NOTE Confidence: 0.98164517

00:50:43.895 --> 00:50:44.795 technical reproducibility

NOTE Confidence: 0.9900421

00:50:45.255 --> 00:50:46.155 between users,

NOTE Confidence: 0.98950845

00:50:46.775 --> 00:50:47.735 in terms of, you know,

NOTE Confidence: 0.98950845

00:50:47.735 --> 00:50:48.235 extracting,

NOTE Confidence: 0.999668

00:50:48.695 --> 00:50:49.195 reliable

NOTE Confidence: 0.9076643

00:50:49.495 --> 00:50:49.995 information,

NOTE Confidence: 0.9735539

00:50:50.535 --> 00:50:51.495 and then, you know, working

NOTE Confidence: 0.9735539

00:50:51.495 --> 00:50:53.195 to translate the the algorithms

NOTE Confidence: 0.9735539

00:50:53.255 --> 00:50:54.614 used to animal models would

NOTE Confidence: 0.9735539

00:50:54.614 --> 00:50:55.320 would be powerful.

NOTE Confidence: 0.9295672

00:50:55.800 --> 00:50:57.320 And engineers love to keep

NOTE Confidence: 0.9295672

00:50:57.320 --> 00:50:58.780 developing, so they they've,

NOTE Confidence: 0.934895

00:50:59.320 --> 00:51:01.080 started to develop additional kind

NOTE Confidence: 0.934895

00:51:01.080 --> 00:51:02.280 of techniques to to do

NOTE Confidence: 0.934895

00:51:02.280 --> 00:51:02.780 similar,

NOTE Confidence: 0.93987453

00:51:04.760 --> 00:51:06.520 data analysis, and that includes,

NOTE Confidence: 0.93987453

00:51:06.760 --> 00:51:08.935 using, NURBS curves for their

NOTE Confidence: 0.93987453

00:51:09.075 --> 00:51:11.175 ability to, make a continuous

NOTE Confidence: 0.93987453

00:51:11.235 --> 00:51:12.295 parametric curve,

NOTE Confidence: 0.9927215

00:51:12.755 --> 00:51:13.655 smoother data,

NOTE Confidence: 0.9247154

00:51:14.195 --> 00:51:15.475 less noise, and then sub

NOTE Confidence: 0.9247154

00:51:15.475 --> 00:51:16.775 pixel diameter measurements.

NOTE Confidence: 0.99005073

00:51:17.395 --> 00:51:18.915 And then expanding further upon

NOTE Confidence: 0.99005073

00:51:18.915 --> 00:51:19.655 that there,

NOTE Confidence: 0.8850868

00:51:20.594 --> 00:51:22.355 we've been working on machine

NOTE Confidence: 0.8850868

00:51:22.355 --> 00:51:22.835 learning,

NOTE Confidence: 0.7858

00:51:23.155 --> 00:51:23.655 development,

NOTE Confidence: 0.9566058

00:51:24.330 --> 00:51:25.630 in order to automatically,

NOTE Confidence: 0.86026263

00:51:26.170 --> 00:51:28.650 segment the aortic root, for

NOTE Confidence: 0.86026263

00:51:28.650 --> 00:51:29.150 analysis,

NOTE Confidence: 0.98801136

00:51:29.610 --> 00:51:30.570 that would be much higher

NOTE Confidence: 0.98801136

00:51:30.570 --> 00:51:31.770 throughput than than what we're

NOTE Confidence: 0.98801136

00:51:31.770 --> 00:51:33.390 doing, currently. So,

NOTE Confidence: 0.9477717

00:51:34.170 --> 00:51:35.210 much work is is going

NOTE Confidence: 0.9477717

00:51:35.210 --> 00:51:36.670 on in that regard.

NOTE Confidence: 0.99483776

00:51:37.235 --> 00:51:37.895 And so,

NOTE Confidence: 0.99768984

00:51:38.594 --> 00:51:39.335 you know,

NOTE Confidence: 0.9715185

00:51:39.875 --> 00:51:41.315 putting things together with what

NOTE Confidence: 0.9715185

00:51:41.315 --> 00:51:42.515 I've shown you today, kind

NOTE Confidence: 0.9715185

00:51:42.515 --> 00:51:43.715 of other data and our

NOTE Confidence: 0.9715185

00:51:43.715 --> 00:51:44.215 data,

NOTE Confidence: 0.9802479

00:51:44.594 --> 00:51:45.715 thinking about how this ties

NOTE Confidence: 0.9802479

00:51:45.715 --> 00:51:47.175 into patient care. Right?

NOTE Confidence: 0.98860395

00:51:47.475 --> 00:51:49.555 And so, you know, trying

NOTE Confidence: 0.98860395

00:51:49.555 --> 00:51:51.050 to to think about how

NOTE Confidence: 0.98860395

00:51:51.050 --> 00:51:52.410 can we develop a better

NOTE Confidence: 0.98860395

00:51:52.410 --> 00:51:54.090 assessment of our patients, especially

NOTE Confidence: 0.98860395

00:51:54.090 --> 00:51:55.070 at early ages,

NOTE Confidence: 0.9694459

00:51:55.370 --> 00:51:56.570 and then inform our our

NOTE Confidence: 0.9694459

00:51:56.570 --> 00:51:58.510 cardiac management decision making

NOTE Confidence: 0.79105544

00:51:58.969 --> 00:51:59.469 accordingly.

NOTE Confidence: 0.9491348

00:52:00.010 --> 00:52:01.530 And so, one approach, you

NOTE Confidence: 0.9491348

00:52:01.530 --> 00:52:02.890 know, we are commonly doing

NOTE Confidence: 0.9491348

00:52:02.890 --> 00:52:04.010 a a TA panel in

NOTE Confidence: 0.9491348

00:52:04.010 --> 00:52:05.050 our patients who come into

NOTE Confidence: 0.9491348

00:52:05.050 --> 00:52:06.925 clinic, with a buccal swab.

NOTE Confidence: 0.9491348

00:52:06.925 --> 00:52:08.285 And we're always doing an

NOTE Confidence: 0.9491348

00:52:08.285 --> 00:52:08.785 echocardiogram,

NOTE Confidence: 0.9690364

00:52:09.244 --> 00:52:11.085 and we're currently measuring, aortic

NOTE Confidence: 0.9690364

00:52:11.085 --> 00:52:11.585 diameters.

NOTE Confidence: 0.9678278

00:52:12.045 --> 00:52:13.244 And so some of the

NOTE Confidence: 0.9678278

00:52:13.244 --> 00:52:14.704 tools that we wanna use,

NOTE Confidence: 0.93863976

00:52:15.325 --> 00:52:16.525 based on our data and

NOTE Confidence: 0.93863976

00:52:16.525 --> 00:52:17.905 research and then ultimately

NOTE Confidence: 0.9565651

00:52:18.560 --> 00:52:19.840 translating into clinic would be

NOTE Confidence: 0.9565651

00:52:19.840 --> 00:52:21.859 genome sequencing combined with transcriptome

NOTE Confidence: 0.9565651

00:52:21.920 --> 00:52:23.280 analysis in order to, you

NOTE Confidence: 0.9565651

00:52:23.280 --> 00:52:24.400 know, twenty only to you

NOTE Confidence: 0.9565651

00:52:24.400 --> 00:52:25.760 know, you know, it's a

NOTE Confidence: 0.9565651

00:52:25.760 --> 00:52:27.200 fraction, you know, anywhere from

NOTE Confidence: 0.9565651

00:52:27.200 --> 00:52:28.160 five to twenty percent of

NOTE Confidence: 0.9565651

00:52:28.160 --> 00:52:29.300 patients who have erotopathy

NOTE Confidence: 0.7599703

00:52:29.760 --> 00:52:31.055 that we are identifying genetic

NOTE Confidence: 0.86512417

00:52:32.395 --> 00:52:33.594 causes. So thinking about how

NOTE Confidence: 0.86512417

00:52:33.594 --> 00:52:34.581 genome plus transcriptome could be

NOTE Confidence: 0.86512417

00:52:34.581 --> 00:52:35.475 a more, robust,

NOTE Confidence: 0.8312607

00:52:35.915 --> 00:52:37.855 a way to, make diagnoses

NOTE Confidence: 0.8312607

00:52:37.994 --> 00:52:39.194 as well as, you know,

NOTE Confidence: 0.8312607

00:52:39.194 --> 00:52:40.315 our development of a variant

NOTE Confidence: 0.8312607

00:52:40.315 --> 00:52:41.214 functional assays.

NOTE Confidence: 0.9725032

00:52:41.594 --> 00:52:42.474 To do that, we you

NOTE Confidence: 0.9725032

00:52:42.474 --> 00:52:43.275 know, I showed you our

NOTE Confidence: 0.9725032

00:52:43.275 --> 00:52:44.875 echo tracking method, which could

NOTE Confidence: 0.9725032

00:52:44.875 --> 00:52:46.015 be, implemented,

NOTE Confidence: 0.8337449

00:52:46.530 --> 00:52:47.030 in,

NOTE Confidence: 0.99248075

00:52:48.210 --> 00:52:49.090 you know, in the coming

NOTE Confidence: 0.99248075

00:52:49.090 --> 00:52:49.590 years.

NOTE Confidence: 0.98236245

00:52:49.969 --> 00:52:50.850 And then, you know, from

NOTE Confidence: 0.98236245

00:52:50.850 --> 00:52:52.450 these data, we're getting information

NOTE Confidence: 0.98236245

00:52:52.450 --> 00:52:54.469 about genetic cause. We're identifying

NOTE Confidence: 0.9245642

00:52:54.850 --> 00:52:56.610 potential genetic modifiers through our

NOTE Confidence: 0.9245642

00:52:56.610 --> 00:52:57.110 studies,

NOTE Confidence: 0.9401609

00:52:57.570 --> 00:52:59.570 and then also identifying structural

NOTE Confidence: 0.9401609

00:52:59.570 --> 00:53:01.655 parameters. So can you, over

NOTE Confidence: 0.9401609

00:53:01.655 --> 00:53:03.494 time, accumulate data that,

NOTE Confidence: 0.963726

00:53:03.815 --> 00:53:05.015 can be integrated into a

NOTE Confidence: 0.963726

00:53:05.015 --> 00:53:06.214 risk classifier, and then we

NOTE Confidence: 0.963726

00:53:06.214 --> 00:53:07.974 can start to stratify cardiac

NOTE Confidence: 0.963726

00:53:07.974 --> 00:53:08.474 management?

NOTE Confidence: 0.86774915

00:53:08.855 --> 00:53:09.895 And really all this is,

NOTE Confidence: 0.86774915

00:53:09.895 --> 00:53:10.214 you know,

NOTE Confidence: 0.94706994

00:53:11.175 --> 00:53:12.875 you know, would be potentially

NOTE Confidence: 0.94706994

00:53:13.015 --> 00:53:14.375 doable when it comes to,

NOTE Confidence: 0.94706994

00:53:14.695 --> 00:53:16.155 the standard clinical workflows.

NOTE Confidence: 0.95092326

00:53:17.400 --> 00:53:18.440 Also, from these data, you

NOTE Confidence: 0.95092326

00:53:18.440 --> 00:53:19.640 know, we're learning about what

NOTE Confidence: 0.95092326

00:53:19.640 --> 00:53:20.359 could be the path of

NOTE Confidence: 0.95092326

00:53:20.359 --> 00:53:22.119 biology of aortic aneurysm and

NOTE Confidence: 0.95092326

00:53:22.119 --> 00:53:23.800 identifying therapeutic targets. And I

NOTE Confidence: 0.95092326

00:53:23.800 --> 00:53:24.680 went through a series of

NOTE Confidence: 0.95092326

00:53:24.680 --> 00:53:26.359 studies in which, overall, I

NOTE Confidence: 0.95092326

00:53:26.359 --> 00:53:27.319 think we're, you know, kind

NOTE Confidence: 0.95092326

00:53:27.319 --> 00:53:27.819 of

NOTE Confidence: 0.94874895

00:53:28.695 --> 00:53:30.215 the picture is one of,

NOTE Confidence: 0.94874895

00:53:30.535 --> 00:53:31.594 you know, metabolic,

NOTE Confidence: 0.9537131

00:53:32.135 --> 00:53:33.575 dysfunction, generally, you know, with

NOTE Confidence: 0.9537131

00:53:33.575 --> 00:53:34.715 oxidative stress,

NOTE Confidence: 0.96093446

00:53:35.015 --> 00:53:36.075 the role for CoQAB,

NOTE Confidence: 0.96428794

00:53:36.775 --> 00:53:38.055 in the smooth muscle cells

NOTE Confidence: 0.96428794

00:53:38.055 --> 00:53:39.675 and other evidence for CoQ

NOTE Confidence: 0.7904412

00:53:39.975 --> 00:53:41.275 ten synthesis genes,

NOTE Confidence: 0.98324865

00:53:41.975 --> 00:53:43.175 the changes in long chain

NOTE Confidence: 0.98324865

00:53:43.175 --> 00:53:44.610 fatty acid acylation that we've

NOTE Confidence: 0.98324865

00:53:44.770 --> 00:53:45.270 identified,

NOTE Confidence: 0.9766411

00:53:45.650 --> 00:53:46.150 lysophosphatidic

NOTE Confidence: 0.91855896

00:53:46.610 --> 00:53:48.050 acid metabolism, and and this

NOTE Confidence: 0.91855896

00:53:48.050 --> 00:53:48.950 candidate gene.

NOTE Confidence: 0.94553214

00:53:49.410 --> 00:53:50.950 So these are, you know,

NOTE Confidence: 0.94553214

00:53:51.090 --> 00:53:52.950 areas of further investigation.

NOTE Confidence: 0.94576406

00:53:53.890 --> 00:53:54.290 And so,

NOTE Confidence: 0.95892584

00:53:54.850 --> 00:53:56.610 these are, many, many people

NOTE Confidence: 0.95892584

00:53:56.610 --> 00:53:58.390 who I've worked with, collaborated,

NOTE Confidence: 0.95892584

00:53:58.530 --> 00:53:59.955 you know, have mentored me.

NOTE Confidence: 0.95892584

00:54:00.195 --> 00:54:01.235 I wanted to point out,

NOTE Confidence: 0.8452156

00:54:01.875 --> 00:54:02.614 Joel Corvera,

NOTE Confidence: 0.9456565

00:54:02.915 --> 00:54:04.835 aortic surgeon at Indiana University,

NOTE Confidence: 0.9456565

00:54:04.835 --> 00:54:05.575 was essential

NOTE Confidence: 0.9460799

00:54:05.955 --> 00:54:07.315 to the collection of aortic

NOTE Confidence: 0.9460799

00:54:07.315 --> 00:54:09.075 tissues, for example. Craig Orgin,

NOTE Confidence: 0.9460799

00:54:09.075 --> 00:54:10.594 who's a a biomedical engineer

NOTE Confidence: 0.9460799

00:54:10.594 --> 00:54:11.655 at Purdue University,

NOTE Confidence: 0.90403426

00:54:12.114 --> 00:54:12.614 cardiovascular

NOTE Confidence: 0.97432375

00:54:12.915 --> 00:54:14.135 imaging research lab.

NOTE Confidence: 0.9037221

00:54:14.890 --> 00:54:15.869 Glenn Iannucci,

NOTE Confidence: 0.9545359

00:54:16.170 --> 00:54:17.690 pediatric cardiologist who leads the

NOTE Confidence: 0.9545359

00:54:17.690 --> 00:54:19.450 aortic center at Emory University,

NOTE Confidence: 0.9545359

00:54:19.450 --> 00:54:20.570 which is our collaborator for

NOTE Confidence: 0.9545359

00:54:20.570 --> 00:54:21.869 a longitudinal study.

NOTE Confidence: 0.907359

00:54:22.410 --> 00:54:24.010 Freddie Damon is a a

NOTE Confidence: 0.907359

00:54:24.010 --> 00:54:26.110 pediatrics resident at Stanford who's,

NOTE Confidence: 0.94540554

00:54:26.535 --> 00:54:27.575 who wrote the code for

NOTE Confidence: 0.94540554

00:54:27.575 --> 00:54:29.015 our tracking algorithm. Shubh is

NOTE Confidence: 0.94540554

00:54:29.015 --> 00:54:30.214 a PhD student who's gonna

NOTE Confidence: 0.94540554

00:54:30.214 --> 00:54:32.155 be coming, next year here,

NOTE Confidence: 0.94540554

00:54:32.454 --> 00:54:33.575 is working on the algorithm

NOTE Confidence: 0.94540554

00:54:33.575 --> 00:54:34.454 as well. And KB was

NOTE Confidence: 0.94540554

00:54:34.454 --> 00:54:35.575 a medical student who did

NOTE Confidence: 0.94540554

00:54:35.575 --> 00:54:36.375 the a lot of the

NOTE Confidence: 0.94540554

00:54:36.375 --> 00:54:36.875 transcriptome

NOTE Confidence: 0.99668574

00:54:37.414 --> 00:54:37.914 data.

NOTE Confidence: 0.9413769

00:54:38.934 --> 00:54:39.434 So,

NOTE Confidence: 0.97021466

00:54:40.839 --> 00:54:41.880 yeah. So thanks for your

NOTE Confidence: 0.97021466

00:54:41.880 --> 00:54:43.320 attention. I really appreciate it.

NOTE Confidence: 0.97021466

00:54:43.320 --> 00:54:44.619 Happy to answer any questions.

NOTE Confidence: 0.6828178

00:54:46.280 --> 00:54:46.520 If if

NOTE Confidence: 0.6987347

00:54:51.719 --> 00:54:53.020 That was really

NOTE Confidence: 0.60090077

00:55:08.529 --> 00:55:09.329 the the hot spot and

NOTE Confidence: 0.60090077

00:55:09.329 --> 00:55:10.609 the variability that we're gonna

NOTE Confidence: 0.60090077

00:55:10.609 --> 00:55:11.829 have to deal

NOTE Confidence: 0.82405746

00:55:12.130 --> 00:55:12.710 with something.

NOTE Confidence: 0.6409188

00:55:13.730 --> 00:55:14.950 And then we just find

NOTE Confidence: 0.6409188

00:55:15.170 --> 00:55:17.109 that to better understand who,

NOTE Confidence: 0.89996463

00:55:19.489 --> 00:55:21.250 segments of the population will

NOTE Confidence: 0.89996463

00:55:21.250 --> 00:55:22.869 have a differential response

NOTE Confidence: 0.7780527

00:55:24.535 --> 00:55:26.295 their, like, their standard treatment

NOTE Confidence: 0.7780527

00:55:26.295 --> 00:55:27.815 should be modified, you know,

NOTE Confidence: 0.7780527

00:55:27.815 --> 00:55:28.955 in other words, are

NOTE Confidence: 0.8886835

00:55:29.335 --> 00:55:31.114 there gene variant treatment

NOTE Confidence: 0.639241

00:55:31.575 --> 00:55:32.075 interaction

NOTE Confidence: 0.24634911

00:55:32.695 --> 00:55:33.195 that

NOTE Confidence: 0.73547804

00:55:35.255 --> 00:55:36.535 could then divide those who

NOTE Confidence: 0.73547804

00:55:36.535 --> 00:55:37.435 are more likely

NOTE Confidence: 0.63424605

00:55:46.330 --> 00:55:47.870 Super super interesting.

NOTE Confidence: 0.97724074

00:55:49.130 --> 00:55:50.330 And I'm very curious if

NOTE Confidence: 0.97724074

00:55:50.330 --> 00:55:50.989 you have

NOTE Confidence: 0.99321353

00:55:51.370 --> 00:55:51.870 any

NOTE Confidence: 0.9080844

00:55:55.155 --> 00:55:57.495 early data on whether there

NOTE Confidence: 0.88730633

00:55:58.355 --> 00:56:00.375 are complications of those patterns

NOTE Confidence: 0.85046625

00:56:00.675 --> 00:56:02.375 that predate likelihood

NOTE Confidence: 0.7064763

00:56:02.755 --> 00:56:04.275 of rupture in other words.

NOTE Confidence: 0.7064763

00:56:04.275 --> 00:56:05.075 You know, I think of

NOTE Confidence: 0.7064763

00:56:05.075 --> 00:56:06.275 the standard way or I

NOTE Confidence: 0.7064763

00:56:06.275 --> 00:56:07.655 think you're fortunate in terms

NOTE Confidence: 0.7064763

00:56:07.795 --> 00:56:08.695 of how to

NOTE Confidence: 0.6784213

00:56:09.869 --> 00:56:10.609 narrow the measurements

NOTE Confidence: 0.85733193

00:56:11.069 --> 00:56:12.049 and our reporting,

NOTE Confidence: 0.99837613

00:56:12.349 --> 00:56:13.089 which is

NOTE Confidence: 0.9210156

00:56:13.469 --> 00:56:15.390 cool. But I'd be very

NOTE Confidence: 0.9210156

00:56:15.390 --> 00:56:16.190 curious to know if you

NOTE Confidence: 0.9210156

00:56:16.190 --> 00:56:17.549 could use that to kinda

NOTE Confidence: 0.9210156

00:56:17.549 --> 00:56:18.589 say, well, this person is

NOTE Confidence: 0.9210156

00:56:18.589 --> 00:56:19.089 likely,

NOTE Confidence: 0.99829334

00:56:19.789 --> 00:56:20.289 you

NOTE Confidence: 0.85749996

00:56:20.910 --> 00:56:22.029 know, there's a change in

NOTE Confidence: 0.85749996

00:56:22.029 --> 00:56:23.710 that pattern that says this

NOTE Confidence: 0.85749996

00:56:23.710 --> 00:56:24.915 is working that needs to

NOTE Confidence: 0.85749996

00:56:25.075 --> 00:56:25.895 go quicker.

NOTE Confidence: 0.9484028

00:56:27.955 --> 00:56:28.995 So with respect to the

NOTE Confidence: 0.9484028

00:56:28.995 --> 00:56:30.275 first question, you are I

NOTE Confidence: 0.9484028

00:56:30.275 --> 00:56:31.175 think the data,

NOTE Confidence: 0.9102144

00:56:31.555 --> 00:56:33.635 tying genotype to the outcome

NOTE Confidence: 0.9102144

00:56:33.635 --> 00:56:34.775 response to therapy

NOTE Confidence: 0.8460072

00:56:35.715 --> 00:56:37.415 is Right. Was a trial

NOTE Confidence: 0.8460072

00:56:37.475 --> 00:56:38.935 called the compare trial,

NOTE Confidence: 0.9711507

00:56:39.235 --> 00:56:40.135 done in Netherlands

NOTE Confidence: 0.9455163

00:56:41.289 --> 00:56:43.049 years ago, maybe, where they

NOTE Confidence: 0.9455163

00:56:43.049 --> 00:56:44.410 they did some some in

NOTE Confidence: 0.9455163

00:56:44.410 --> 00:56:45.849 vitro work to classify the

NOTE Confidence: 0.9455163

00:56:45.849 --> 00:56:47.069 FBN one variance.

NOTE Confidence: 0.30623206

00:56:48.089 --> 00:56:48.589 This

NOTE Confidence: 0.9097804

00:56:49.450 --> 00:56:49.950 is,

NOTE Confidence: 0.6167343

00:56:50.329 --> 00:56:51.210 like, we've done.

NOTE Confidence: 0.97580206

00:56:52.809 --> 00:56:54.250 And then they they did

NOTE Confidence: 0.97580206

00:56:54.250 --> 00:56:54.915 they did,

NOTE Confidence: 0.99663

00:56:55.315 --> 00:56:55.815 suggest

NOTE Confidence: 0.6973031

00:56:56.275 --> 00:56:58.775 that the, wasartan would patients

NOTE Confidence: 0.6973031

00:56:58.875 --> 00:56:59.975 would likely

NOTE Confidence: 0.38869077

00:57:00.594 --> 00:57:01.094 be.

NOTE Confidence: 0.8369803

00:57:06.995 --> 00:57:08.995 So that's an example. I

NOTE Confidence: 0.8369803

00:57:08.995 --> 00:57:09.495 think,

NOTE Confidence: 0.9177961

00:57:11.849 --> 00:57:12.650 you know, it's,

NOTE Confidence: 0.96719295

00:57:13.289 --> 00:57:14.510 when it comes to genotype

NOTE Confidence: 0.96719295

00:57:14.650 --> 00:57:15.150 outcomes,

NOTE Confidence: 0.91804206

00:57:16.170 --> 00:57:17.130 also, you know, some of

NOTE Confidence: 0.91804206

00:57:17.130 --> 00:57:18.349 these more recent multitudes,

NOTE Confidence: 0.8646143

00:57:20.329 --> 00:57:22.250 consortium studies have started to

NOTE Confidence: 0.8646143

00:57:22.250 --> 00:57:23.690 look at what's, you know,

NOTE Confidence: 0.8646143

00:57:23.690 --> 00:57:24.970 after the pair, what's the

NOTE Confidence: 0.8646143

00:57:24.970 --> 00:57:27.055 likelihood of of population, and

NOTE Confidence: 0.8646143

00:57:27.055 --> 00:57:28.595 how does a genetic diagnosis

NOTE Confidence: 0.3652686

00:57:29.295 --> 00:57:30.415 have the the

NOTE Confidence: 0.33763653

00:57:31.375 --> 00:57:32.195 those workplace

NOTE Confidence: 0.5693223

00:57:33.135 --> 00:57:34.525 or a sort of simple.

NOTE Confidence: 0.72040397

00:57:39.930 --> 00:57:41.630 Probably emerging data in the.

NOTE Confidence: 0.84209293

00:57:43.610 --> 00:57:44.490 You know, in terms of

NOTE Confidence: 0.84209293

00:57:44.490 --> 00:57:46.190 the you know? Yes. Absolutely.

NOTE Confidence: 0.84209293

00:57:46.250 --> 00:57:47.530 So I think everybody knows

NOTE Confidence: 0.84209293

00:57:47.530 --> 00:57:48.890 that you would for issues

NOTE Confidence: 0.84209293

00:57:48.890 --> 00:57:50.250 that have an aortic rupture,

NOTE Confidence: 0.84209293

00:57:50.250 --> 00:57:51.230 this section is

NOTE Confidence: 0.73585355

00:57:51.755 --> 00:57:53.375 more complicated than just the

NOTE Confidence: 0.74759084

00:57:53.755 --> 00:57:55.195 size, which is the the

NOTE Confidence: 0.74759084

00:57:55.195 --> 00:57:55.695 approach.

NOTE Confidence: 0.82405764

00:57:56.315 --> 00:57:58.235 And and so we'd be

NOTE Confidence: 0.82405764

00:57:58.235 --> 00:57:59.755 very interested to begin to

NOTE Confidence: 0.82405764

00:57:59.755 --> 00:58:01.055 look at those,

NOTE Confidence: 0.68283284

00:58:01.355 --> 00:58:03.035 you know, who have echo

NOTE Confidence: 0.68283284

00:58:03.035 --> 00:58:04.655 data and the fact that

NOTE Confidence: 0.59363526

00:58:05.330 --> 00:58:06.950 with outcomes. You know, echo.

NOTE Confidence: 0.59363526

00:58:07.170 --> 00:58:08.470 You know, there's other data.

NOTE Confidence: 0.6839371

00:58:08.850 --> 00:58:10.550 We We started to discuss,

NOTE Confidence: 0.6839371

00:58:10.690 --> 00:58:12.290 and and outcome distribution. They're

NOTE Confidence: 0.6839371

00:58:12.290 --> 00:58:14.390 very interesting. We have, recently,

NOTE Confidence: 0.86252195

00:58:15.490 --> 00:58:16.370 you know, we're just not

NOTE Confidence: 0.86252195

00:58:16.370 --> 00:58:17.650 to to start, but instead

NOTE Confidence: 0.86252195

00:58:17.650 --> 00:58:18.230 of transthoracic

NOTE Confidence: 0.97083455

00:58:18.530 --> 00:58:19.030 echo,

NOTE Confidence: 0.7999017

00:58:19.570 --> 00:58:21.110 using TDE data,

NOTE Confidence: 0.95299983

00:58:21.705 --> 00:58:22.685 in in

NOTE Confidence: 0.60887074

00:58:23.465 --> 00:58:23.965 the

NOTE Confidence: 0.45059928

00:58:25.465 --> 00:58:25.965 OR,

NOTE Confidence: 0.7966918

00:58:27.865 --> 00:58:29.225 run the run run our

NOTE Confidence: 0.7966918

00:58:29.225 --> 00:58:30.365 test, our math,

NOTE Confidence: 0.83778334

00:58:30.825 --> 00:58:32.285 on the air vision

NOTE Confidence: 0.49561492

00:58:33.225 --> 00:58:33.725 properties.

NOTE Confidence: 0.9158887

00:58:34.750 --> 00:58:36.670 Maybe some ability to definitely

NOTE Confidence: 0.9158887

00:58:36.670 --> 00:58:38.030 ability to monitor blood pressure

NOTE Confidence: 0.9158887

00:58:38.030 --> 00:58:38.850 real time,

NOTE Confidence: 0.75160414

00:58:39.230 --> 00:58:40.590 you know, for extraction of

NOTE Confidence: 0.75160414

00:58:40.590 --> 00:58:42.210 of of properties such,

NOTE Confidence: 0.94918054

00:58:42.910 --> 00:58:43.570 but also,

NOTE Confidence: 0.9948993

00:58:43.950 --> 00:58:45.490 you know, a very robust

NOTE Confidence: 0.6775582

00:58:45.790 --> 00:58:48.210 approach to tissue collection. You

NOTE Confidence: 0.9020026

00:58:49.595 --> 00:58:50.875 know, as we're thinking about,

NOTE Confidence: 0.9020026

00:58:50.875 --> 00:58:51.375 does,

NOTE Confidence: 0.9934829

00:58:51.755 --> 00:58:52.414 a certain

NOTE Confidence: 0.9842731

00:58:52.714 --> 00:58:53.214 dysfunction

NOTE Confidence: 0.94904774

00:58:53.515 --> 00:58:54.394 in the aortic,

NOTE Confidence: 0.70164317

00:58:54.954 --> 00:58:55.454 dynamics,

NOTE Confidence: 0.9284131

00:58:56.315 --> 00:58:58.075 correlate with a certain type

NOTE Confidence: 0.9284131

00:58:58.075 --> 00:58:59.934 of tissue abnormality, whether it's.

NOTE Confidence: 0.9026292

00:59:05.650 --> 00:59:07.350 Yeah. That that that that's,

NOTE Confidence: 0.9026292

00:59:07.570 --> 00:59:08.530 Here he is. I'm walking

NOTE Confidence: 0.9026292

00:59:08.530 --> 00:59:10.290 over to Jeff here. You

NOTE Confidence: 0.9026292

00:59:10.290 --> 00:59:11.810 mentioned in one slides the

NOTE Confidence: 0.9026292

00:59:11.810 --> 00:59:12.950 potential for IPS.

NOTE Confidence: 0.8914819

00:59:13.410 --> 00:59:14.950 Well, so I'm curious what

NOTE Confidence: 0.8914819

00:59:15.170 --> 00:59:16.210 I'm very curious what you

NOTE Confidence: 0.8914819

00:59:16.210 --> 00:59:16.869 do, and

NOTE Confidence: 0.7507485

00:59:17.170 --> 00:59:18.690 we have, obviously, connection within

NOTE Confidence: 0.7507485

00:59:18.690 --> 00:59:19.970 the CRC with the to

NOTE Confidence: 0.7507485

00:59:19.970 --> 00:59:21.270 support that could work.

NOTE Confidence: 0.99515736

00:59:22.665 --> 00:59:24.425 Yeah. No. I think, absolutely.

NOTE Confidence: 0.99515736

00:59:24.425 --> 00:59:25.385 I think, you know, if

NOTE Confidence: 0.99515736

00:59:25.385 --> 00:59:26.445 we wanted to

NOTE Confidence: 0.960212

00:59:27.705 --> 00:59:29.005 to optimize our

NOTE Confidence: 0.88901716

00:59:29.545 --> 00:59:30.925 the approach when it comes

NOTE Confidence: 0.88901716

00:59:30.985 --> 00:59:31.645 to scriptional

NOTE Confidence: 0.8268321

00:59:32.025 --> 00:59:34.345 analysis or the interpretation of

NOTE Confidence: 0.8268321

00:59:34.345 --> 00:59:35.825 variants, you know, we need,

NOTE Confidence: 0.8268321

00:59:35.825 --> 00:59:37.305 you know, we can't get

NOTE Confidence: 0.8268321

00:59:37.305 --> 00:59:38.319 all the information we would

NOTE Confidence: 0.8268321

00:59:38.319 --> 00:59:39.380 need with a blood sample.

NOTE Confidence: 0.8268321

00:59:39.440 --> 00:59:40.400 So in patients who are

NOTE Confidence: 0.8268321

00:59:40.400 --> 00:59:40.900 preoperative,

NOTE Confidence: 0.8044297

00:59:41.200 --> 00:59:41.920 you know, we could we

NOTE Confidence: 0.8044297

00:59:41.920 --> 00:59:42.400 could,

NOTE Confidence: 0.5523002

00:59:42.800 --> 00:59:44.260 generate the packing cells,

NOTE Confidence: 0.67998713

00:59:44.880 --> 00:59:46.579 for the the two part

NOTE Confidence: 0.67998713

00:59:46.720 --> 00:59:47.700 molecular assessments

NOTE Confidence: 0.52051896

00:59:48.160 --> 00:59:49.380 to try to to correlate.

NOTE Confidence: 0.6755343

00:59:55.295 --> 00:59:56.175 As well as, you know,

NOTE Confidence: 0.6755343

00:59:56.175 --> 00:59:58.415 obviously, the ability to to

NOTE Confidence: 0.6755343

00:59:58.415 --> 01:00:00.435 to to preserve the system.

NOTE Confidence: 0.94157934

01:00:09.990 --> 01:00:10.490 Congratulations.

NOTE Confidence: 0.5971118

01:00:10.950 --> 01:00:11.690 That's so

NOTE Confidence: 0.28732154

01:00:12.069 --> 01:00:13.589 and you're with with this

NOTE Confidence: 0.28732154

01:00:13.589 --> 01:00:14.089 really

NOTE Confidence: 0.74899465

01:00:14.869 --> 01:00:16.010 pretty much work.

NOTE Confidence: 0.8976016

01:00:16.789 --> 01:00:18.630 No questions about a lot

NOTE Confidence: 0.8976016

01:00:18.630 --> 01:00:20.650 of these genetic in connections

NOTE Confidence: 0.6883316

01:00:20.950 --> 01:00:22.595 to air top feet.

NOTE Confidence: 0.8426315

01:00:23.535 --> 01:00:24.335 I I guess

NOTE Confidence: 0.99584794

01:00:24.974 --> 01:00:25.775 and I have a lot

NOTE Confidence: 0.99584794

01:00:25.775 --> 01:00:26.895 of questions, but I'll ask

NOTE Confidence: 0.99584794

01:00:26.895 --> 01:00:28.915 one, sort of general question.

NOTE Confidence: 0.96396947

01:00:29.375 --> 01:00:30.895 When I hear a talk

NOTE Confidence: 0.96396947

01:00:30.895 --> 01:00:32.835 where there are ten, sometimes

NOTE Confidence: 0.96396947

01:00:33.055 --> 01:00:34.734 hundreds of genes and gene

NOTE Confidence: 0.96396947

01:00:34.734 --> 01:00:35.234 modifiers

NOTE Confidence: 0.88079816

01:00:36.010 --> 01:00:37.870 that result in not identical

NOTE Confidence: 0.88079816

01:00:37.930 --> 01:00:38.750 but similar

NOTE Confidence: 0.96966857

01:00:39.690 --> 01:00:41.870 pathology or pathologic phenotypes.

NOTE Confidence: 0.98090804

01:00:42.330 --> 01:00:44.010 I always wonder, like, there's

NOTE Confidence: 0.98090804

01:00:44.010 --> 01:00:45.550 got to be a common

NOTE Confidence: 0.93365633

01:00:46.090 --> 01:00:46.590 pathophysiologic

NOTE Confidence: 0.9995266

01:00:47.450 --> 01:00:47.950 driver

NOTE Confidence: 0.89867634

01:00:48.705 --> 01:00:50.305 of the of the phenotype

NOTE Confidence: 0.89867634

01:00:50.305 --> 01:00:51.845 of the aortic dilatation

NOTE Confidence: 0.7849976

01:00:52.305 --> 01:00:54.085 and that and the dissection.

NOTE Confidence: 0.5757248

01:00:54.445 --> 01:00:54.945 You

NOTE Confidence: 0.5915042

01:00:55.305 --> 01:00:55.805 mentioned,

NOTE Confidence: 0.77973676

01:00:57.025 --> 01:00:57.525 issues.

NOTE Confidence: 0.993658

01:00:59.345 --> 01:01:01.125 You mentioned oxidative stress.

NOTE Confidence: 0.9411872

01:01:01.425 --> 01:01:03.125 Is there anything about,

NOTE Confidence: 0.9646185

01:01:04.109 --> 01:01:04.609 mechanosensing

NOTE Confidence: 0.9902468

01:01:05.470 --> 01:01:06.289 of the

NOTE Confidence: 0.9554889

01:01:06.589 --> 01:01:07.089 aorta

NOTE Confidence: 0.99295276

01:01:07.390 --> 01:01:09.710 in its abnormal state that

NOTE Confidence: 0.99295276

01:01:09.710 --> 01:01:10.210 drives,

NOTE Confidence: 0.93047637

01:01:10.829 --> 01:01:12.430 you know, the oxidative stress

NOTE Confidence: 0.93047637

01:01:12.430 --> 01:01:14.430 or might drive inflammation, which

NOTE Confidence: 0.93047637

01:01:14.430 --> 01:01:16.130 you didn't talk about much

NOTE Confidence: 0.93047637

01:01:16.349 --> 01:01:17.490 that I have to mention?

NOTE Confidence: 0.9771681

01:01:25.335 --> 01:01:27.175 Yeah. So absolutely. So Jay

NOTE Confidence: 0.9771681

01:01:27.175 --> 01:01:27.675 Humphrey,

NOTE Confidence: 0.74563336

01:01:29.015 --> 01:01:30.055 here at at Yale and

NOTE Confidence: 0.74563336

01:01:30.055 --> 01:01:30.555 then

NOTE Confidence: 0.650772

01:01:31.415 --> 01:01:32.725 she did a really

NOTE Confidence: 0.68359333

01:01:33.410 --> 01:01:34.290 nice paper with Diane and

NOTE Confidence: 0.68359333

01:01:34.290 --> 01:01:34.790 Melowitz

NOTE Confidence: 0.69123566

01:01:36.050 --> 01:01:37.570 thinking about how the smooth

NOTE Confidence: 0.69123566

01:01:37.570 --> 01:01:39.330 muscle cells, using these these

NOTE Confidence: 0.69123566

01:01:39.330 --> 01:01:40.710 things could be,

NOTE Confidence: 0.9762618

01:01:41.170 --> 01:01:42.130 when you look at the

NOTE Confidence: 0.9762618

01:01:42.130 --> 01:01:43.270 spectrum of genes,

NOTE Confidence: 0.79965526

01:01:43.570 --> 01:01:44.470 could be a

NOTE Confidence: 0.63814396

01:01:45.495 --> 01:01:46.875 kind of functionality

NOTE Confidence: 0.59695333

01:01:47.255 --> 01:01:48.555 or a degree of how

NOTE Confidence: 0.59695333

01:01:48.775 --> 01:01:49.995 mechanics and

NOTE Confidence: 0.70582694

01:01:50.655 --> 01:01:52.315 I mean, it's,

NOTE Confidence: 0.88722074

01:01:55.735 --> 01:01:57.255 remains to be done. So

NOTE Confidence: 0.88722074

01:01:57.255 --> 01:01:58.215 this was this was just

NOTE Confidence: 0.88722074

01:01:58.215 --> 01:01:58.935 a site I've used in

NOTE Confidence: 0.88722074

01:01:58.935 --> 01:02:00.215 the past, but kinda kinda

NOTE Confidence: 0.88722074

01:02:00.215 --> 01:02:01.170 highlights some of that where

NOTE Confidence: 0.88722074

01:02:01.170 --> 01:02:01.829 you you

NOTE Confidence: 0.88597965

01:02:02.130 --> 01:02:03.670 have the smooth muscle cells,

NOTE Confidence: 0.7807855

01:02:04.130 --> 01:02:06.309 sensing force generating force

NOTE Confidence: 0.9184133

01:02:07.410 --> 01:02:08.690 in the tissue, but then,

NOTE Confidence: 0.9184133

01:02:08.690 --> 01:02:09.349 you know, obviously,

NOTE Confidence: 0.6252747

01:02:10.849 --> 01:02:12.130 do the extra tether matrix

NOTE Confidence: 0.6252747

01:02:12.130 --> 01:02:12.630 and

NOTE Confidence: 0.9823056

01:02:13.055 --> 01:02:14.495 how is how is that

NOTE Confidence: 0.9823056

01:02:14.495 --> 01:02:15.535 contributing? So I think that

NOTE Confidence: 0.9823056

01:02:15.535 --> 01:02:16.035 that's,

NOTE Confidence: 0.7425399

01:02:17.375 --> 01:02:18.415 yeah, I think that that's,

NOTE Confidence: 0.7425399

01:02:18.415 --> 01:02:19.315 like, path

NOTE Confidence: 0.8858845

01:02:19.935 --> 01:02:21.855 to shore. Right? You're absolutely

NOTE Confidence: 0.8858845

01:02:21.855 --> 01:02:23.375 right. It'd be terrific to

NOTE Confidence: 0.8858845

01:02:23.375 --> 01:02:24.355 find a common,

NOTE Confidence: 0.52573514

01:02:25.135 --> 01:02:25.635 happiness.

NOTE Confidence: 0.8855559

01:02:26.880 --> 01:02:28.480 And I think as we're

NOTE Confidence: 0.8855559

01:02:28.799 --> 01:02:30.500 it's a it's a challenge

NOTE Confidence: 0.8855559

01:02:30.559 --> 01:02:31.760 when our when our human

NOTE Confidence: 0.8855559

01:02:31.760 --> 01:02:32.260 studies,

NOTE Confidence: 0.8767028

01:02:33.040 --> 01:02:35.140 because we have such, heterogeneity

NOTE Confidence: 0.8767028

01:02:35.200 --> 01:02:36.420 as genetic heterogeneity.

NOTE Confidence: 0.96441114

01:02:36.799 --> 01:02:37.700 Patient heterogeneity.

NOTE Confidence: 0.3840202

01:02:39.005 --> 01:02:39.585 But we

NOTE Confidence: 0.92886937

01:02:40.045 --> 01:02:41.665 see, you know, associations.

NOTE Confidence: 0.6770076

01:02:41.965 --> 01:02:43.565 We can hone in. This

NOTE Confidence: 0.6770076

01:02:43.565 --> 01:02:44.385 is genetic.

NOTE Confidence: 0.86873037

01:02:44.765 --> 01:02:46.285 We're not. And it see

NOTE Confidence: 0.86873037

01:02:46.285 --> 01:02:47.565 associations. It it raises the

NOTE Confidence: 0.86873037

01:02:47.565 --> 01:02:48.525 possibility that what you guys

NOTE Confidence: 0.86873037

01:02:48.525 --> 01:02:49.325 are it's,

NOTE Confidence: 0.84954

01:02:49.725 --> 01:02:50.705 relatively common.

NOTE Confidence: 0.8099787

01:02:51.565 --> 01:02:52.610 You know, so I I

NOTE Confidence: 0.8099787

01:02:52.610 --> 01:02:54.210 think, there's there's a lot

NOTE Confidence: 0.8099787

01:02:54.210 --> 01:02:55.730 of work. Yeah. Yeah. To

NOTE Confidence: 0.8099787

01:02:55.730 --> 01:02:57.170 be done. Just try to

NOTE Confidence: 0.8099787

01:02:57.170 --> 01:02:59.350 to solve solve that problem.

NOTE Confidence: 0.8099787

01:02:59.410 --> 01:03:00.530 I mean, you know, eighty

NOTE Confidence: 0.8099787

01:03:00.530 --> 01:03:01.730 percent in kids, we use

NOTE Confidence: 0.8099787

01:03:01.730 --> 01:03:02.470 eighty percent.

NOTE Confidence: 0.69572634

01:03:06.345 --> 01:03:07.725 Which is really very rationalist.

NOTE Confidence: 0.6458038

01:03:08.265 --> 01:03:09.725 Rationalist developed in markets.

NOTE Confidence: 0.44350612

01:03:10.425 --> 01:03:11.645 It's a big trap.

NOTE Confidence: 0.62186664

01:03:12.105 --> 01:03:12.605 And

NOTE Confidence: 0.87432146

01:03:13.225 --> 01:03:14.585 and if probably affect it.

NOTE Confidence: 0.87432146

01:03:14.585 --> 01:03:15.385 You know? Your day is

NOTE Confidence: 0.87432146

01:03:15.385 --> 01:03:16.985 not. But, I mean, it's

NOTE Confidence: 0.87432146

01:03:17.065 --> 01:03:18.025 you know? You can get

NOTE Confidence: 0.87432146

01:03:18.025 --> 01:03:18.985 at it, you know, that

NOTE Confidence: 0.87432146

01:03:18.985 --> 01:03:19.805 type of question.

NOTE Confidence: 0.8736528

01:03:20.390 --> 01:03:21.050 I'm sorry.

NOTE Confidence: 0.5982053

01:03:22.750 --> 01:03:23.250 It's.

NOTE Confidence: 0.58828735

01:03:24.950 --> 01:03:25.610 And inflammation?

NOTE Confidence: 0.92164946

01:03:26.070 --> 01:03:27.750 Yeah. I, I see kids,

NOTE Confidence: 0.92164946

01:03:27.750 --> 01:03:28.390 so we don't see a

NOTE Confidence: 0.92164946

01:03:28.390 --> 01:03:29.670 lot of the you know,

NOTE Confidence: 0.92164946

01:03:29.670 --> 01:03:31.050 it's not a delayed

NOTE Confidence: 0.7634922

01:03:32.230 --> 01:03:33.510 age largely. I know there's

NOTE Confidence: 0.7634922

01:03:33.510 --> 01:03:35.610 some House house, man, which,

NOTE Confidence: 0.7634922

01:03:35.855 --> 01:03:36.734 you know, I'm not sure

NOTE Confidence: 0.7634922

01:03:36.734 --> 01:03:38.494 how physiologically relevant they are.

NOTE Confidence: 0.7634922

01:03:38.494 --> 01:03:39.395 It's a

NOTE Confidence: 0.6299914

01:03:39.855 --> 01:03:41.075 very, kind of, robust,

NOTE Confidence: 0.33206812

01:03:42.174 --> 01:03:42.674 mandatory,

NOTE Confidence: 0.10976938

01:03:43.694 --> 01:03:44.194 and

NOTE Confidence: 0.7520048

01:03:44.974 --> 01:03:45.714 then it's

NOTE Confidence: 0.5814992

01:03:46.575 --> 01:03:48.355 just also mechanism dissection.

NOTE Confidence: 0.7182296

01:03:50.400 --> 01:03:51.780 Maybe last question, Bayaria.

NOTE Confidence: 0.926516

01:03:52.480 --> 01:03:53.680 Yeah. Actually, my question is

NOTE Confidence: 0.926516

01:03:53.680 --> 01:03:55.040 very similar to this. And,

NOTE Confidence: 0.926516

01:03:55.119 --> 01:03:57.119 you mentioned that this, calcium

NOTE Confidence: 0.926516

01:03:57.119 --> 01:03:58.339 sensing I mean,

NOTE Confidence: 0.8605124

01:03:59.119 --> 01:04:00.720 calcium channel TRP v two,

NOTE Confidence: 0.8605124

01:04:00.720 --> 01:04:01.700 which is a mechanosensing

NOTE Confidence: 0.8943176

01:04:02.079 --> 01:04:02.579 channel,

NOTE Confidence: 0.8576029

01:04:03.040 --> 01:04:03.780 is increased,

NOTE Confidence: 0.87904096

01:04:04.560 --> 01:04:06.365 in expression of that. Have

NOTE Confidence: 0.87904096

01:04:06.365 --> 01:04:07.325 you looked at the other

NOTE Confidence: 0.87904096

01:04:07.325 --> 01:04:08.605 diseases you see in similar

NOTE Confidence: 0.87904096

01:04:08.605 --> 01:04:10.204 pattern you find so that

NOTE Confidence: 0.87904096

01:04:10.204 --> 01:04:11.244 you can have a common

NOTE Confidence: 0.87904096

01:04:11.244 --> 01:04:12.445 pathway? And another thing is

NOTE Confidence: 0.87904096

01:04:12.445 --> 01:04:13.025 a mitochondrial

NOTE Confidence: 0.9175258

01:04:13.325 --> 01:04:14.605 disease that you have. The

NOTE Confidence: 0.9175258

01:04:14.605 --> 01:04:15.984 link is actually unclear.

NOTE Confidence: 0.919436

01:04:16.365 --> 01:04:17.325 But have you looked at

NOTE Confidence: 0.919436

01:04:17.325 --> 01:04:18.204 the other ones such as,

NOTE Confidence: 0.919436

01:04:18.204 --> 01:04:19.805 you know, TGF beta receptor

NOTE Confidence: 0.919436

01:04:19.805 --> 01:04:20.305 mutations?

NOTE Confidence: 0.916055

01:04:20.930 --> 01:04:22.310 If they have the same,

NOTE Confidence: 0.916055

01:04:22.370 --> 01:04:23.250 and can you link that

NOTE Confidence: 0.916055

01:04:23.250 --> 01:04:24.870 to, like, your TGF signaling

NOTE Confidence: 0.9425165

01:04:25.570 --> 01:04:26.770 as a common because there

NOTE Confidence: 0.9425165

01:04:26.770 --> 01:04:27.670 are a lot of them

NOTE Confidence: 0.7270293

01:04:29.010 --> 01:04:29.910 in that pathway,

NOTE Confidence: 0.8843119

01:04:30.690 --> 01:04:31.810 to see. And and then

NOTE Confidence: 0.8843119

01:04:31.810 --> 01:04:33.170 finally, the question is that

NOTE Confidence: 0.8843119

01:04:33.170 --> 01:04:34.310 if there is a mechanosensing

NOTE Confidence: 0.7787442

01:04:34.770 --> 01:04:36.070 and it has some you

NOTE Confidence: 0.7787442

01:04:36.075 --> 01:04:37.115 know, channel is actually a

NOTE Confidence: 0.7787442

01:04:37.115 --> 01:04:38.335 mechanosensing channel,

NOTE Confidence: 0.86007

01:04:38.635 --> 01:04:39.915 why did you fail with

NOTE Confidence: 0.86007

01:04:39.915 --> 01:04:41.595 the treatment of these? And

NOTE Confidence: 0.86007

01:04:41.595 --> 01:04:42.555 have you ever looked to

NOTE Confidence: 0.86007

01:04:42.555 --> 01:04:44.255 see, actually, these these genotype

NOTE Confidence: 0.86007

01:04:44.315 --> 01:04:45.435 specific to people who like

NOTE Confidence: 0.86007

01:04:45.435 --> 01:04:46.954 to have higher expression of

NOTE Confidence: 0.86007

01:04:46.954 --> 01:04:48.315 TRP v two? Do you

NOTE Confidence: 0.86007

01:04:48.315 --> 01:04:49.915 see an association in response

NOTE Confidence: 0.86007

01:04:49.915 --> 01:04:51.214 to treatment that reduces

NOTE Confidence: 0.9937309

01:04:51.880 --> 01:04:52.460 blood pressure?

NOTE Confidence: 0.995978

01:04:52.920 --> 01:04:53.420 Thank

NOTE Confidence: 0.99965197

01:04:56.760 --> 01:04:57.260 you.

NOTE Confidence: 0.9374027

01:04:57.800 --> 01:04:58.300 So

NOTE Confidence: 0.899648

01:04:58.680 --> 01:04:59.960 Right. So so with respect

NOTE Confidence: 0.899648

01:04:59.960 --> 01:05:01.400 to TRPV two, it's, you

NOTE Confidence: 0.899648

01:05:01.400 --> 01:05:03.240 know, that's a observation in

NOTE Confidence: 0.899648

01:05:03.240 --> 01:05:04.380 in Marfan syndrome,

NOTE Confidence: 0.3013127

01:05:05.145 --> 01:05:06.045 and when you see mutations.

NOTE Confidence: 0.82563907

01:05:06.825 --> 01:05:08.105 All these. So I think

NOTE Confidence: 0.82563907

01:05:08.105 --> 01:05:08.765 it warrants

NOTE Confidence: 0.9925283

01:05:09.385 --> 01:05:10.125 more investigation

NOTE Confidence: 0.9944215

01:05:10.585 --> 01:05:11.325 in in

NOTE Confidence: 0.98812306

01:05:11.785 --> 01:05:12.925 across populations.

NOTE Confidence: 0.97749066

01:05:14.585 --> 01:05:15.385 You know, I think,

NOTE Confidence: 0.97738385

01:05:16.185 --> 01:05:17.965 we can continue to investigate

NOTE Confidence: 0.97738385

01:05:18.185 --> 01:05:19.480 that with our, you know,

NOTE Confidence: 0.97738385

01:05:19.480 --> 01:05:21.480 larger cohort of mRNA seek

NOTE Confidence: 0.97738385

01:05:21.480 --> 01:05:22.460 data, for example.

NOTE Confidence: 0.8729769

01:05:22.920 --> 01:05:24.400 We just haven't gotten that

NOTE Confidence: 0.8729769

01:05:24.760 --> 01:05:26.700 got to that point yet.

NOTE Confidence: 0.9864161

01:05:28.520 --> 01:05:30.040 You know, mitochondrial the role

NOTE Confidence: 0.9864161

01:05:30.040 --> 01:05:31.480 for mitochondria, you know, there's

NOTE Confidence: 0.9864161

01:05:31.480 --> 01:05:33.080 some evidence in mouse models

NOTE Confidence: 0.9864161

01:05:33.080 --> 01:05:34.360 that was pretty compelling when

NOTE Confidence: 0.9864161

01:05:34.360 --> 01:05:35.575 it came to the,

NOTE Confidence: 0.90587926

01:05:36.195 --> 01:05:37.575 connection between the,

NOTE Confidence: 0.9377338

01:05:38.435 --> 01:05:39.415 each other matrix

NOTE Confidence: 0.8680421

01:05:40.035 --> 01:05:40.535 dysfunction

NOTE Confidence: 0.9815057

01:05:40.915 --> 01:05:42.295 and the links between

NOTE Confidence: 0.8999418

01:05:42.835 --> 01:05:44.275 the across the membrane to

NOTE Confidence: 0.8999418

01:05:44.275 --> 01:05:44.935 the bladder.

NOTE Confidence: 0.16481553

01:05:46.115 --> 01:05:46.615 And

NOTE Confidence: 0.95883673

01:05:47.075 --> 01:05:48.515 that's that remains to these.

NOTE Confidence: 0.95883673

01:05:48.515 --> 01:05:49.560 I mean, I would say,

NOTE Confidence: 0.9686409

01:05:50.120 --> 01:05:51.260 you know, we do see

NOTE Confidence: 0.9686409

01:05:51.320 --> 01:05:53.000 it's mild mild aortic root

NOTE Confidence: 0.9686409

01:05:53.000 --> 01:05:54.300 dilation in in

NOTE Confidence: 0.9250811

01:05:54.600 --> 01:05:56.860 kids who have, genetic mitochondrial

NOTE Confidence: 0.9250811

01:05:57.000 --> 01:05:58.600 disease. You know, thinking about

NOTE Confidence: 0.9250811

01:05:58.600 --> 01:06:00.280 how, you know, a piece

NOTE Confidence: 0.9250811

01:06:00.280 --> 01:06:01.980 of evidence for, you know,

NOTE Confidence: 0.4976894

01:06:02.605 --> 01:06:03.565 cut out is of the

NOTE Confidence: 0.4976894

01:06:03.565 --> 01:06:04.065 situation.

NOTE Confidence: 0.4589962

01:06:05.525 --> 01:06:06.025 And

NOTE Confidence: 0.9096256

01:06:07.485 --> 01:06:07.985 so

NOTE Confidence: 0.9164762

01:06:09.645 --> 01:06:10.605 Ben, can I ask a

NOTE Confidence: 0.9164762

01:06:10.605 --> 01:06:11.345 quick question?

NOTE Confidence: 0.9972394

01:06:11.805 --> 01:06:12.305 Yes.

NOTE Confidence: 0.9926971

01:06:13.805 --> 01:06:14.785 Exciting talk.

NOTE Confidence: 0.8454967

01:06:15.180 --> 01:06:16.460 Yeah. As Eric mentioned, we

NOTE Confidence: 0.8454967

01:06:16.460 --> 01:06:19.020 could provide IPSC engineering, tissue

NOTE Confidence: 0.8454967

01:06:19.020 --> 01:06:20.780 engineering to generate a small

NOTE Confidence: 0.8454967

01:06:20.780 --> 01:06:22.140 muscle tissue for you to

NOTE Confidence: 0.8454967

01:06:22.140 --> 01:06:23.200 study your disease.

NOTE Confidence: 0.935959

01:06:23.740 --> 01:06:24.940 I have a question about,

NOTE Confidence: 0.935959

01:06:25.260 --> 01:06:26.480 oxidative phosphorylation.

NOTE Confidence: 0.7692621

01:06:27.275 --> 01:06:28.955 So we also observe in

NOTE Confidence: 0.7692621

01:06:28.955 --> 01:06:29.855 our early diagnosis,

NOTE Confidence: 0.77427095

01:06:30.315 --> 01:06:31.995 iPS cells, small cells. We

NOTE Confidence: 0.77427095

01:06:31.995 --> 01:06:34.315 observe abnormal loss production. What

NOTE Confidence: 0.77427095

01:06:34.315 --> 01:06:35.755 are your thoughts about why

NOTE Confidence: 0.77427095

01:06:35.755 --> 01:06:37.755 this aneurysm is to know

NOTE Confidence: 0.77427095

01:06:37.915 --> 01:06:39.675 stenosis is small cells. They

NOTE Confidence: 0.77427095

01:06:39.675 --> 01:06:40.315 tend to have,

NOTE Confidence: 0.9896103

01:06:53.615 --> 01:06:55.214 a reasonable place to start

NOTE Confidence: 0.9896103

01:06:55.214 --> 01:06:56.994 with with that is is,

NOTE Confidence: 0.9363351

01:06:57.855 --> 01:06:58.595 an abrogation

NOTE Confidence: 0.8319356

01:06:59.375 --> 01:06:59.855 in,

NOTE Confidence: 0.98926973

01:07:00.175 --> 01:07:01.555 gene expression that,

NOTE Confidence: 0.95812273

01:07:02.015 --> 01:07:03.234 is, you know,

NOTE Confidence: 0.98596144

01:07:05.450 --> 01:07:06.829 required to mitigate,

NOTE Confidence: 0.99566174

01:07:07.609 --> 01:07:09.069 you know, to to

NOTE Confidence: 0.77833265

01:07:10.170 --> 01:07:10.670 temper

NOTE Confidence: 0.95756215

01:07:10.970 --> 01:07:12.970 oxidative stress and reactive oxygen

NOTE Confidence: 0.95756215

01:07:12.970 --> 01:07:13.470 species?

NOTE Confidence: 0.9834402

01:07:14.490 --> 01:07:15.609 You know, is there a

NOTE Confidence: 0.9834402

01:07:15.609 --> 01:07:16.109 mitochondrial,

NOTE Confidence: 0.71090746

01:07:17.130 --> 01:07:17.630 dysfunction,

NOTE Confidence: 0.9973368

01:07:18.170 --> 01:07:18.670 dysfunction

NOTE Confidence: 0.95683885

01:07:18.970 --> 01:07:20.349 in aerobic respiration

NOTE Confidence: 0.9876564

01:07:20.895 --> 01:07:21.875 that leads to,

NOTE Confidence: 0.99179846

01:07:22.575 --> 01:07:23.635 spurious generation

NOTE Confidence: 0.9803866

01:07:23.935 --> 01:07:26.115 of, of, free radicals.

NOTE Confidence: 0.9955285

01:07:27.055 --> 01:07:28.335 There's some data that, you

NOTE Confidence: 0.9955285

01:07:28.335 --> 01:07:28.835 know,

NOTE Confidence: 0.988863

01:07:29.135 --> 01:07:31.075 could be potentially related to,

NOTE Confidence: 0.9988973

01:07:31.455 --> 01:07:31.955 angiotensin

NOTE Confidence: 0.9240042

01:07:32.335 --> 01:07:33.315 receptor signaling,

NOTE Confidence: 0.95322555

01:07:34.335 --> 01:07:35.635 you know, that cascade,

NOTE Confidence: 0.9797567

01:07:36.440 --> 01:07:38.940 leading to increased generation of

NOTE Confidence: 0.9797567

01:07:39.079 --> 01:07:39.900 of of ROS.

NOTE Confidence: 0.91045773

01:07:40.920 --> 01:07:41.799 Those are my thoughts right

NOTE Confidence: 0.91045773

01:07:41.799 --> 01:07:43.079 now, but I'm excited about

NOTE Confidence: 0.91045773

01:07:43.079 --> 01:07:44.440 the, IPS cell, as you

NOTE Confidence: 0.91045773

01:07:44.440 --> 01:07:44.940 mentioned.

NOTE Confidence: 0.9219811

01:07:45.559 --> 01:07:47.239 Great. Well, critical Thank you.

NOTE Confidence: 0.9219811

01:07:47.319 --> 01:07:48.920 Thank you for, teaching us,

NOTE Confidence: 0.9219811

01:07:49.160 --> 01:07:50.299 here, and

NOTE Confidence: 0.52267087

01:07:51.095 --> 01:07:52.474 brave enough to work.

NOTE Confidence: 0.6261975

01:07:52.934 --> 01:07:53.734 I'll do it now. So

NOTE Confidence: 0.6261975

01:07:53.734 --> 01:07:55.335 thank you for the, and,

NOTE Confidence: 0.6261975

01:07:55.654 --> 01:07:57.434 hopefully, I believe you heard

NOTE Confidence: 0.5055968

01:07:57.734 --> 01:07:58.714 some technical collaborations

NOTE Confidence: 0.7491098

01:07:59.335 --> 01:08:00.694 between our section and departments

NOTE Confidence: 0.7491098

01:08:00.694 --> 01:08:01.335 on its work,

NOTE Confidence: 0.76506406

01:08:01.815 --> 01:08:03.734 and, representing here how it

NOTE Confidence: 0.76506406

01:08:03.734 --> 01:08:05.575 proceeds over the. Thank you,

NOTE Confidence: 0.76506406

01:08:05.575 --> 01:08:06.075 Luis.

NOTE Confidence: 0.94629943

01:08:06.410 --> 01:08:07.370 Thank you so much. Thanks,

NOTE Confidence: 0.94629943

01:08:07.370 --> 01:08:08.750 Adrian. Thank you.