WEBVTT

NOTE duration: ”01:00:25.320”

NOTE Confidence: 0.6417155

00:01:23.069 --> 00:01:23.569 Yeah.

NOTE Confidence: 0.8225597

00:03:08.335 --> 00:03:09.455 It's, like, a lot harder

NOTE Confidence: 0.8225597

00:03:09.455 --> 00:03:10.895 for it than for any

NOTE Confidence: 0.8225597

00:03:10.895 --> 00:03:11.395 other.

NOTE Confidence: 0.789199

00:03:12.095 --> 00:03:12.595 Right?

NOTE Confidence: 0.59121203

00:03:30.345 --> 00:03:30.845 It's

NOTE Confidence: 0.29197592

00:03:37.312 --> 00:03:37.812 a

NOTE Confidence: 0.7884516

00:04:38.345 --> 00:04:40.045 Yeah. Okay. Welcome, everybody.

NOTE Confidence: 0.95741767

00:04:41.705 --> 00:04:42.925 We'll just get started.

NOTE Confidence: 0.89781505

00:04:43.410 --> 00:04:44.310 Here's a CME

NOTE Confidence: 0.99824035

00:04:45.490 --> 00:04:45.990 code.

NOTE Confidence: 0.9021348

00:04:47.170 --> 00:04:47.670 K.

NOTE Confidence: 0.986912

00:04:48.210 --> 00:04:50.210 Just the upcoming schedule for

NOTE Confidence: 0.986912

00:04:50.210 --> 00:04:51.430 the next couple weeks.

NOTE Confidence: 0.994553

00:04:52.130 --> 00:04:53.330 You can see next week

NOTE Confidence: 0.994553

00:04:53.330 --> 00:04:54.550 is doctor Pelletier,

NOTE Confidence: 0.92573345

00:04:55.410 --> 00:04:57.110 doctor Petrie from the UK.

NOTE Confidence: 0.9018015

00:04:57.455 --> 00:04:58.654 And we'll have another EP

NOTE Confidence: 0.9018015

00:04:58.654 --> 00:04:59.955 clinical case conference.

NOTE Confidence: 0.97348547

00:05:01.295 --> 00:05:03.295 And then upcoming in later

NOTE Confidence: 0.97348547

00:05:03.295 --> 00:05:03.955 in November

NOTE Confidence: 0.99333847

00:05:04.255 --> 00:05:04.735 is,

NOTE Confidence: 0.89520514

00:05:05.214 --> 00:05:07.235 Todd Valenis, which is our,

NOTE Confidence: 0.96828717

00:05:07.935 --> 00:05:09.775 imaging symposium that same day.

NOTE Confidence: 0.96828717

00:05:09.775 --> 00:05:10.335 That will be in the

NOTE Confidence: 0.96828717

00:05:10.335 --> 00:05:11.154 Park Auditorium.

NOTE Confidence: 0.8838425

00:05:11.960 --> 00:05:12.839 Just a note there. And

NOTE Confidence: 0.8838425

00:05:12.839 --> 00:05:14.120 then the Zarratt lecture as

NOTE Confidence: 0.8838425

00:05:14.120 --> 00:05:14.620 well.

NOTE Confidence: 0.9974013

00:05:18.760 --> 00:05:19.880 Okay. So I'll start off

NOTE Confidence: 0.9974013

00:05:19.880 --> 00:05:21.900 today by introducing our dynamic

NOTE Confidence: 0.9974013

00:05:21.960 --> 00:05:22.460 duo,

NOTE Confidence: 0.9080405

00:05:22.920 --> 00:05:24.600 doctor Gallegos and doctor Abu

NOTE Confidence: 0.9080405

00:05:24.600 --> 00:05:25.100 Alawi.

NOTE Confidence: 0.9589451

00:05:25.685 --> 00:05:26.885 So it's my pleasure to

NOTE Confidence: 0.9589451

00:05:26.885 --> 00:05:28.985 introduce doctor Sarah Abu Alawi,

NOTE Confidence: 0.98517984

00:05:29.445 --> 00:05:30.485 a third year fellow here

NOTE Confidence: 0.98517984

00:05:30.485 --> 00:05:31.225 at Yale.

NOTE Confidence: 0.9507839

00:05:31.685 --> 00:05:32.964 She earned her medical degree

NOTE Confidence: 0.9507839

00:05:32.964 --> 00:05:34.425 with honors from the American

NOTE Confidence: 0.9507839

00:05:34.485 --> 00:05:36.085 University of Beirut where she

NOTE Confidence: 0.9507839

00:05:36.085 --> 00:05:37.605 was inducted into the AOA

NOTE Confidence: 0.9507839

00:05:37.605 --> 00:05:39.605 Honor Medical Society and received

NOTE Confidence: 0.9507839

00:05:39.605 --> 00:05:41.940 the prestigious Penro Penrose Award

NOTE Confidence: 0.9507839

00:05:41.940 --> 00:05:44.040 for excellence in scholarship, leadership,

NOTE Confidence: 0.9507839

00:05:44.339 --> 00:05:46.360 and contributions to university life.

NOTE Confidence: 0.99962616

00:05:47.140 --> 00:05:49.240 Following medical school, she pursued

NOTE Confidence: 0.83776855

00:05:50.180 --> 00:05:51.400 postdoctoral research

NOTE Confidence: 0.98235255

00:05:51.779 --> 00:05:53.640 at Dana Farber Cancer Institute

NOTE Confidence: 0.98235255

00:05:53.700 --> 00:05:55.240 at the Harvard Medical School,

NOTE Confidence: 0.9985217

00:05:55.865 --> 00:05:57.245 where she focused on epigenetic

NOTE Confidence: 0.9985217

00:05:57.464 --> 00:05:58.605 landscape of genitourinary

NOTE Confidence: 0.99939245

00:05:59.225 --> 00:06:01.385 cancers. Her research contributions have

NOTE Confidence: 0.99939245

00:06:01.385 --> 00:06:02.125 been recognized

NOTE Confidence: 0.9726688

00:06:03.305 --> 00:06:04.365 in leading publications

NOTE Confidence: 0.80192107

00:06:04.665 --> 00:06:05.645 in nature communication,

NOTE Confidence: 0.9948715

00:06:05.945 --> 00:06:07.245 cell cancer, and circulation.

NOTE Confidence: 0.90361005

00:06:08.370 --> 00:06:09.730 She then completed her internal

NOTE Confidence: 0.90361005

00:06:09.730 --> 00:06:10.230 residency

NOTE Confidence: 0.9522336

00:06:11.170 --> 00:06:12.690 at Brigham and Women's where

NOTE Confidence: 0.9522336

00:06:12.690 --> 00:06:13.970 she also served as chief

NOTE Confidence: 0.9522336

00:06:13.970 --> 00:06:14.950 medical resident.

NOTE Confidence: 0.9883518

00:06:15.330 --> 00:06:17.010 She has received multiple teaching

NOTE Confidence: 0.9883518

00:06:17.010 --> 00:06:18.630 and clinical excellence awards.

NOTE Confidence: 0.9737124

00:06:19.330 --> 00:06:20.950 Currently now as a cardiology

NOTE Confidence: 0.9737124

00:06:21.010 --> 00:06:22.529 fellow here at Yale, her

NOTE Confidence: 0.9737124

00:06:22.529 --> 00:06:24.070 training has focused on advanced

NOTE Confidence: 0.9737124

00:06:24.105 --> 00:06:25.464 imaging and genetics with a

NOTE Confidence: 0.9737124

00:06:25.464 --> 00:06:27.485 special interest in inherited cardiomyopathies.

NOTE Confidence: 0.9728508

00:06:28.585 --> 00:06:29.964 Her research to the Yale

NOTE Confidence: 0.9728508

00:06:30.025 --> 00:06:32.205 card cards data science lab

NOTE Confidence: 0.9728508

00:06:32.425 --> 00:06:34.345 leverages machine learning and AI

NOTE Confidence: 0.9728508

00:06:34.345 --> 00:06:36.045 to integrate genetics and imaging

NOTE Confidence: 0.9728508

00:06:36.265 --> 00:06:37.645 for improved risk stratification,

NOTE Confidence: 0.9973315

00:06:38.410 --> 00:06:40.670 outcome prediction, and personalized therapy

NOTE Confidence: 0.9973315

00:06:40.810 --> 00:06:42.029 in patients with cardiomyopathies.

NOTE Confidence: 0.9626858

00:06:43.050 --> 00:06:44.250 In addition to her research

NOTE Confidence: 0.9626858

00:06:44.250 --> 00:06:45.450 and clinical work, she is

NOTE Confidence: 0.9626858

00:06:45.450 --> 00:06:46.570 an active member of the

NOTE Confidence: 0.9626858

00:06:46.570 --> 00:06:48.490 Yale Women in Cardiology Group

NOTE Confidence: 0.9626858

00:06:48.490 --> 00:06:49.930 and has been recognized as

NOTE Confidence: 0.9626858

00:06:49.930 --> 00:06:51.210 the consultant of the month

NOTE Confidence: 0.9626858

00:06:51.210 --> 00:06:53.230 by Yale's emergency medicine department.

NOTE Confidence: 0.9658644

00:06:55.314 --> 00:06:57.154 Now her mentor, doctor Cecilia

NOTE Confidence: 0.9658644

00:06:57.154 --> 00:06:58.754 Gallegos, is an assistant professor

NOTE Confidence: 0.9658644

00:06:58.754 --> 00:06:59.414 of medicine.

NOTE Confidence: 0.9151885

00:06:59.794 --> 00:07:01.474 She graduated summa cum laude

NOTE Confidence: 0.9151885

00:07:01.474 --> 00:07:03.814 from the Universidad National, Ajitama

NOTE Confidence: 0.9151885

00:07:03.875 --> 00:07:05.634 de Honduras, where she endured

NOTE Confidence: 0.9151885

00:07:05.634 --> 00:07:06.835 and and earned her medical

NOTE Confidence: 0.9151885

00:07:06.835 --> 00:07:07.170 degree.

NOTE Confidence: 0.97250575

00:07:07.730 --> 00:07:09.410 She then completed residency and

NOTE Confidence: 0.97250575

00:07:09.410 --> 00:07:11.110 chief residency at the University

NOTE Confidence: 0.97250575

00:07:11.170 --> 00:07:12.610 of Miami Miller School of

NOTE Confidence: 0.97250575

00:07:12.610 --> 00:07:13.110 Medicine.

NOTE Confidence: 0.979495

00:07:13.570 --> 00:07:15.170 Her academic pursuits brought her

NOTE Confidence: 0.979495

00:07:15.170 --> 00:07:16.690 to Yale, where she completed

NOTE Confidence: 0.979495

00:07:16.690 --> 00:07:18.770 general and advanced cardiology special

NOTE Confidence: 0.979495

00:07:19.010 --> 00:07:19.510 fellowships

NOTE Confidence: 0.94460547

00:07:19.890 --> 00:07:20.630 with specialization

NOTE Confidence: 0.981029

00:07:20.930 --> 00:07:23.065 in advanced cardiac imaging and

NOTE Confidence: 0.981029

00:07:23.065 --> 00:07:24.125 infiltrative cardiomyopathies.

NOTE Confidence: 0.96301633

00:07:25.545 --> 00:07:26.985 She's also served as chief

NOTE Confidence: 0.96301633

00:07:26.985 --> 00:07:27.485 fellow.

NOTE Confidence: 0.99594146

00:07:28.025 --> 00:07:29.225 During her training, she was

NOTE Confidence: 0.99594146

00:07:29.225 --> 00:07:30.825 awarded a master's in health

NOTE Confidence: 0.99594146

00:07:30.825 --> 00:07:32.185 science degree from the Yale

NOTE Confidence: 0.99594146

00:07:32.185 --> 00:07:33.005 School of Medicine

NOTE Confidence: 0.8741615

00:07:33.385 --> 00:07:34.005 with a thesis focused on

NOTE Confidence: 0.8741615

00:07:34.005 --> 00:07:34.238 PET tracers and diagnosis of

NOTE Confidence: 0.8741615

00:07:34.238 --> 00:07:34.925 angiographic stenosis. Her work resulted

NOTE Confidence: 0.57277524

00:07:36.105 --> 00:07:36.980 in co

NOTE Confidence: 0.9929858

00:07:38.260 --> 00:07:38.760 directs

NOTE Confidence: 0.98243594

00:07:40.041 --> 00:07:40.541 the

NOTE Confidence: 0.9842402

00:07:41.822 --> 00:07:42.322 Yale

NOTE Confidence: 0.5186144

00:07:43.602 --> 00:07:44.102 cardiac

NOTE Confidence: 0.9994818

00:07:45.383 --> 00:07:45.883 amyloidosis

NOTE Confidence: 0.85379505

00:07:47.164 --> 00:07:47.664 program

NOTE Confidence: 0.9378977

00:07:49.025 --> 00:07:50.625 programs and co directs the

NOTE Confidence: 0.9378977

00:07:50.625 --> 00:07:53.105 Yale cardiac amyloidosis program where

NOTE Confidence: 0.9378977

00:07:53.105 --> 00:07:54.805 she leads multiple clinical trials.

NOTE Confidence: 0.99934417

00:07:55.425 --> 00:07:56.965 Her current area of research

NOTE Confidence: 0.9347183

00:07:57.265 --> 00:07:59.105 is in transtheretin stability and

NOTE Confidence: 0.9347183

00:07:59.105 --> 00:07:59.605 microvascular

NOTE Confidence: 0.98790115

00:07:59.985 --> 00:08:01.285 dysfunction in amyloidosis.

NOTE Confidence: 0.9455139

00:08:02.310 --> 00:08:03.509 Outside of her clinical and

NOTE Confidence: 0.9455139

00:08:03.509 --> 00:08:05.189 research interests, doctor Glaios has

NOTE Confidence: 0.9455139

00:08:05.189 --> 00:08:06.870 a lifelong passion for medical

NOTE Confidence: 0.9455139

00:08:06.870 --> 00:08:08.949 education and teaching and serves

NOTE Confidence: 0.9455139

00:08:08.949 --> 00:08:10.469 as a program director for

NOTE Confidence: 0.9455139

00:08:10.469 --> 00:08:11.210 the cardiology

NOTE Confidence: 0.91396606

00:08:11.669 --> 00:08:14.265 cardiology imaging specialist fellowship and

NOTE Confidence: 0.91396606

00:08:14.265 --> 00:08:15.865 and the associate program director

NOTE Confidence: 0.91396606

00:08:15.865 --> 00:08:17.305 for the general cardiology fellow

NOTE Confidence: 0.91396606

00:08:17.305 --> 00:08:18.905 as well. Now please join

NOTE Confidence: 0.91396606

00:08:18.905 --> 00:08:20.825 me in welcoming doctor Sarah

NOTE Confidence: 0.91396606

00:08:20.825 --> 00:08:21.645 Abu Alawi.

NOTE Confidence: 0.9825284

00:08:28.600 --> 00:08:30.120 Good afternoon, everyone. Thank you,

NOTE Confidence: 0.9825284

00:08:30.120 --> 00:08:31.240 doctor Clark, for the kind

NOTE Confidence: 0.9825284

00:08:31.240 --> 00:08:32.600 introduction and everyone for being

NOTE Confidence: 0.9825284

00:08:32.600 --> 00:08:33.100 here.

NOTE Confidence: 0.99101466

00:08:33.559 --> 00:08:34.059 So

NOTE Confidence: 0.9367251

00:08:34.520 --> 00:08:36.120 my title, the title of

NOTE Confidence: 0.9367251

00:08:36.120 --> 00:08:37.400 my talk today is Beyond

NOTE Confidence: 0.9367251

00:08:37.400 --> 00:08:38.860 Imaging and Cardiac Amyloidosis.

NOTE Confidence: 0.9898742

00:08:39.894 --> 00:08:40.855 And as many of you

NOTE Confidence: 0.9898742

00:08:40.855 --> 00:08:43.274 know, cardiac amyloidosis has historically

NOTE Confidence: 0.9898742

00:08:43.334 --> 00:08:45.255 been considered a rare and

NOTE Confidence: 0.9898742

00:08:45.255 --> 00:08:46.475 a late stage diagnosis,

NOTE Confidence: 0.99919647

00:08:47.015 --> 00:08:48.695 one that often becomes apparent

NOTE Confidence: 0.99919647

00:08:48.695 --> 00:08:50.535 only when imaging findings are

NOTE Confidence: 0.99919647

00:08:50.535 --> 00:08:51.035 unmistakable.

NOTE Confidence: 0.9986689

00:08:51.780 --> 00:08:53.220 But over the past decade

NOTE Confidence: 0.9986689

00:08:53.220 --> 00:08:54.820 or so, our understanding of

NOTE Confidence: 0.9986689

00:08:54.820 --> 00:08:57.220 amyloid biology and detection has

NOTE Confidence: 0.9986689

00:08:57.220 --> 00:08:58.360 dramatically transformed.

NOTE Confidence: 0.99885744

00:08:58.980 --> 00:09:00.260 And in this talk, I

NOTE Confidence: 0.99885744

00:09:00.260 --> 00:09:02.120 hope to explore emerging biomarkers,

NOTE Confidence: 0.99885744

00:09:02.260 --> 00:09:04.100 molecular tracers, and AI driven

NOTE Confidence: 0.99885744

00:09:04.100 --> 00:09:05.445 tools that may allow us

NOTE Confidence: 0.99885744

00:09:05.445 --> 00:09:06.184 to identify

NOTE Confidence: 0.9658469

00:09:06.565 --> 00:09:08.404 and risk stratify patients long

NOTE Confidence: 0.9658469

00:09:08.404 --> 00:09:10.565 before traditional imaging does with

NOTE Confidence: 0.9658469

00:09:10.565 --> 00:09:11.684 the goal of moving from

NOTE Confidence: 0.9658469

00:09:11.684 --> 00:09:12.184 detection

NOTE Confidence: 0.9448586

00:09:12.804 --> 00:09:15.385 to prediction and ultimately prevention

NOTE Confidence: 0.9448586

00:09:15.445 --> 00:09:16.584 of amyloid cardiomyopathy.

NOTE Confidence: 0.9965154

00:09:18.404 --> 00:09:19.464 This is our disclosures.

NOTE Confidence: 0.9936244

00:09:21.740 --> 00:09:23.260 So for the objectives of

NOTE Confidence: 0.9936244

00:09:23.260 --> 00:09:25.900 today's session, first, we'll briefly

NOTE Confidence: 0.9936244

00:09:25.900 --> 00:09:26.960 describe the pathophysiology

NOTE Confidence: 0.9396251

00:09:27.340 --> 00:09:28.940 and the clinical presentation of

NOTE Confidence: 0.9396251

00:09:28.940 --> 00:09:30.000 inherited transthyretin

NOTE Confidence: 0.98939484

00:09:30.380 --> 00:09:31.200 cardiac amyloidosis

NOTE Confidence: 0.8822928

00:09:31.820 --> 00:09:33.740 focusing on whose specific variants

NOTE Confidence: 0.8822928

00:09:33.740 --> 00:09:35.200 influence disease phenotype.

NOTE Confidence: 0.9246107

00:09:35.875 --> 00:09:37.154 Then we will illustrate the

NOTE Confidence: 0.9246107

00:09:37.154 --> 00:09:39.175 natural progression and transthyretin

NOTE Confidence: 0.8875339

00:09:39.634 --> 00:09:41.975 cardiac amyloidosis from early molecular

NOTE Confidence: 0.8875339

00:09:42.194 --> 00:09:44.214 dies the from early molecular

NOTE Confidence: 0.8875339

00:09:44.355 --> 00:09:44.855 misfolding

NOTE Confidence: 0.9739646

00:09:45.235 --> 00:09:47.014 to avert cardiac involvement.

NOTE Confidence: 0.87588847

00:09:48.000 --> 00:09:48.660 And finally,

NOTE Confidence: 0.9937326

00:09:49.280 --> 00:09:50.660 we will discuss the limitation

NOTE Confidence: 0.9950928

00:09:51.040 --> 00:09:52.720 of current imaging tools and

NOTE Confidence: 0.9950928

00:09:52.720 --> 00:09:54.340 explore how emerging biomarkers

NOTE Confidence: 0.9721953

00:09:55.040 --> 00:09:56.400 allow us to detect disease

NOTE Confidence: 0.9721953

00:09:56.400 --> 00:09:58.880 earlier even before traditional imaging

NOTE Confidence: 0.9721953

00:09:58.880 --> 00:09:59.780 becomes positive.

NOTE Confidence: 0.9764531

00:10:01.245 --> 00:10:03.024 So with that, let's introduce

NOTE Confidence: 0.9764531

00:10:03.084 --> 00:10:03.824 our case,

NOTE Confidence: 0.97887766

00:10:04.125 --> 00:10:05.485 which is the case of

NOTE Confidence: 0.97887766

00:10:05.485 --> 00:10:06.524 a sixty eight year old

NOTE Confidence: 0.97887766

00:10:06.524 --> 00:10:08.704 woman who presented to clinic

NOTE Confidence: 0.97887766

00:10:08.764 --> 00:10:09.964 after being found to have

NOTE Confidence: 0.97887766

00:10:09.964 --> 00:10:11.345 a pathogenic transthyretin

NOTE Confidence: 0.98452646

00:10:11.725 --> 00:10:13.820 variant, which was identified through

NOTE Confidence: 0.98452646

00:10:13.820 --> 00:10:15.740 cascade genetic testing after one

NOTE Confidence: 0.98452646

00:10:15.740 --> 00:10:17.519 of her sons was diagnosed

NOTE Confidence: 0.98452646

00:10:17.580 --> 00:10:19.519 with sarcomereic hypertrophic cardiomyopathy.

NOTE Confidence: 0.99226844

00:10:20.540 --> 00:10:21.500 So she comes to your

NOTE Confidence: 0.99226844

00:10:21.500 --> 00:10:23.839 amyloid clinic entirely asymptomatic

NOTE Confidence: 0.9701947

00:10:24.380 --> 00:10:26.140 yet very concerned about her

NOTE Confidence: 0.9701947

00:10:26.140 --> 00:10:27.679 abnormal genetic test results.

NOTE Confidence: 0.97830206

00:10:28.285 --> 00:10:29.725 And her case raises the

NOTE Confidence: 0.97830206

00:10:29.725 --> 00:10:30.925 key question that will frame

NOTE Confidence: 0.97830206

00:10:30.925 --> 00:10:32.845 today's talk. How do we

NOTE Confidence: 0.97830206

00:10:32.845 --> 00:10:34.365 care for someone in whom

NOTE Confidence: 0.97830206

00:10:34.365 --> 00:10:35.665 the gene speaks first

NOTE Confidence: 0.97315985

00:10:36.045 --> 00:10:37.885 before the phenotype, before the

NOTE Confidence: 0.97315985

00:10:37.885 --> 00:10:39.565 imaging, and before the disease

NOTE Confidence: 0.97315985

00:10:39.565 --> 00:10:40.545 declares itself?

NOTE Confidence: 0.9846823

00:10:41.679 --> 00:10:42.720 So these are the the

NOTE Confidence: 0.9846823

00:10:42.720 --> 00:10:44.260 results of her genetic testing.

NOTE Confidence: 0.9846823

00:10:44.320 --> 00:10:45.280 As you can see, she

NOTE Confidence: 0.9846823

00:10:45.280 --> 00:10:46.179 has a heterozygous,

NOTE Confidence: 0.94607663

00:10:47.280 --> 00:10:49.760 variant in TTR gene, which

NOTE Confidence: 0.94607663

00:10:49.760 --> 00:10:51.200 is specifically the val one

NOTE Confidence: 0.94607663

00:10:51.200 --> 00:10:52.179 forty two isoleucine,

NOTE Confidence: 0.9902965

00:10:52.640 --> 00:10:53.760 also referred to as the

NOTE Confidence: 0.9902965

00:10:53.760 --> 00:10:55.140 val one twenty two isoleucine,

NOTE Confidence: 0.9902965

00:10:55.280 --> 00:10:56.820 which I will refer to

NOTE Confidence: 0.8808487

00:10:57.225 --> 00:10:57.725 interchangeably.

NOTE Confidence: 0.9981711

00:10:58.265 --> 00:10:59.865 And it's a relatively common

NOTE Confidence: 0.9981711

00:10:59.865 --> 00:11:01.865 variant in individuals of African

NOTE Confidence: 0.9981711

00:11:01.865 --> 00:11:03.385 ancestry and known to increase

NOTE Confidence: 0.9981711

00:11:03.385 --> 00:11:04.904 the risk of developing late

NOTE Confidence: 0.9981711

00:11:04.904 --> 00:11:06.204 onset cardiac amyloidosis.

NOTE Confidence: 0.9393851

00:11:08.345 --> 00:11:10.500 This schematic shows the entirety

NOTE Confidence: 0.9393851

00:11:10.500 --> 00:11:12.100 of the TTR coding regions

NOTE Confidence: 0.9393851

00:11:12.100 --> 00:11:13.220 along with some of the

NOTE Confidence: 0.9393851

00:11:13.220 --> 00:11:14.740 variants that have been described,

NOTE Confidence: 0.9393851

00:11:14.740 --> 00:11:15.940 and more than one thirty

NOTE Confidence: 0.9393851

00:11:15.940 --> 00:11:17.620 trans thylethan variants have been

NOTE Confidence: 0.9393851

00:11:17.620 --> 00:11:19.940 described to date, each mostly

NOTE Confidence: 0.9393851

00:11:19.940 --> 00:11:21.320 and by and large representing

NOTE Confidence: 0.9393851

00:11:21.460 --> 00:11:23.255 a single amino acid substitution

NOTE Confidence: 0.99899155

00:11:23.635 --> 00:11:25.014 that can alter the stability

NOTE Confidence: 0.99899155

00:11:25.154 --> 00:11:26.514 of the tetramer in unique

NOTE Confidence: 0.99899155

00:11:26.514 --> 00:11:28.695 ways. And what's really remarkable

NOTE Confidence: 0.99899155

00:11:28.834 --> 00:11:29.894 is how specific

NOTE Confidence: 0.9889471

00:11:30.355 --> 00:11:32.595 substitutions tend to cluster with

NOTE Confidence: 0.9889471

00:11:32.595 --> 00:11:33.975 distinct clinical phenotypes,

NOTE Confidence: 0.9945386

00:11:34.490 --> 00:11:35.709 some primarily neuropathics,

NOTE Confidence: 0.9588307

00:11:36.250 --> 00:11:38.490 other predominantly cardiac, and even

NOTE Confidence: 0.9588307

00:11:38.490 --> 00:11:39.949 some others being protective.

NOTE Confidence: 0.99699247

00:11:41.290 --> 00:11:42.649 Let's focus a little bit

NOTE Confidence: 0.99699247

00:11:42.649 --> 00:11:43.790 on some of the TTR

NOTE Confidence: 0.99699247

00:11:43.850 --> 00:11:45.949 variants that are well defined

NOTE Confidence: 0.99807173

00:11:46.250 --> 00:11:47.709 and are rather common.

NOTE Confidence: 0.97826463

00:11:48.315 --> 00:11:49.595 So on the right hand

NOTE Confidence: 0.97826463

00:11:49.595 --> 00:11:50.554 side over here is the

NOTE Confidence: 0.97826463

00:11:50.554 --> 00:11:51.855 val one twenty two isoleucine,

NOTE Confidence: 0.97826463

00:11:52.155 --> 00:11:53.195 which is a variant that

NOTE Confidence: 0.97826463

00:11:53.195 --> 00:11:55.195 our patient has. And it's

NOTE Confidence: 0.97826463

00:11:55.195 --> 00:11:56.554 estimated to be prevalent in

NOTE Confidence: 0.97826463

00:11:56.554 --> 00:11:57.934 about three to four percent

NOTE Confidence: 0.97826463

00:11:57.995 --> 00:11:59.535 of African American individuals.

NOTE Confidence: 0.9875335

00:12:00.075 --> 00:12:01.695 Typically, it is late onset.

NOTE Confidence: 0.9875335

00:12:01.755 --> 00:12:03.295 It's predominantly cardiac,

NOTE Confidence: 0.9978439

00:12:04.120 --> 00:12:05.559 with an estimated up to

NOTE Confidence: 0.9978439

00:12:05.559 --> 00:12:07.000 a hundred percent penetrance in

NOTE Confidence: 0.9978439

00:12:07.000 --> 00:12:08.120 patients over the age of

NOTE Confidence: 0.9978439

00:12:08.120 --> 00:12:08.939 sixty five

NOTE Confidence: 0.95487505

00:12:09.240 --> 00:12:10.759 and usually affecting more males

NOTE Confidence: 0.95487505

00:12:10.759 --> 00:12:11.420 than females.

NOTE Confidence: 0.9435935

00:12:12.439 --> 00:12:14.360 Other well described variants include

NOTE Confidence: 0.9435935

00:12:14.360 --> 00:12:16.360 the val thirty MET, which

NOTE Confidence: 0.9435935

00:12:16.360 --> 00:12:17.879 is overall the most common

NOTE Confidence: 0.9435935

00:12:17.879 --> 00:12:18.379 worldwide.

NOTE Confidence: 0.9196384

00:12:19.095 --> 00:12:20.774 It actually presents in an

NOTE Confidence: 0.9196384

00:12:20.774 --> 00:12:22.454 endemic form in Sweden and

NOTE Confidence: 0.9196384

00:12:22.454 --> 00:12:22.954 Portugal,

NOTE Confidence: 0.98246956

00:12:23.654 --> 00:12:25.415 and presents mostly with an

NOTE Confidence: 0.98246956

00:12:25.415 --> 00:12:27.894 early onset neuropathic phenotype, but

NOTE Confidence: 0.98246956

00:12:27.894 --> 00:12:29.095 can also present in non

NOTE Confidence: 0.98246956

00:12:29.095 --> 00:12:30.695 endemic regions with a mixed

NOTE Confidence: 0.98246956

00:12:30.695 --> 00:12:32.795 cardiac and neuropathic phenotype.

NOTE Confidence: 0.9265989

00:12:33.770 --> 00:12:35.230 And then also the threonine

NOTE Confidence: 0.9265989

00:12:35.370 --> 00:12:37.290 sixty ala, which is prevalent

NOTE Confidence: 0.9265989

00:12:37.290 --> 00:12:38.250 in about one percent in

NOTE Confidence: 0.9265989

00:12:38.250 --> 00:12:39.370 the County Donegal in the

NOTE Confidence: 0.9265989

00:12:39.370 --> 00:12:40.590 Republic of Ireland,

NOTE Confidence: 0.97577626

00:12:41.130 --> 00:12:42.170 with an age of onset

NOTE Confidence: 0.97577626

00:12:42.170 --> 00:12:44.330 typically after fifty and also

NOTE Confidence: 0.97577626

00:12:44.330 --> 00:12:46.350 a mixed cardiac and neurologic

NOTE Confidence: 0.97577626

00:12:46.410 --> 00:12:46.910 phenotype.

NOTE Confidence: 0.97798353

00:12:48.554 --> 00:12:49.754 And so with that, I

NOTE Confidence: 0.97798353

00:12:49.754 --> 00:12:51.274 also wanna highlight some other

NOTE Confidence: 0.97798353

00:12:51.274 --> 00:12:53.194 protective TTR variants, which are

NOTE Confidence: 0.97798353

00:12:53.194 --> 00:12:55.675 rare but actually modulate disease

NOTE Confidence: 0.97798353

00:12:55.675 --> 00:12:57.615 risk in carriers of amyloidogenic

NOTE Confidence: 0.96634495

00:12:58.074 --> 00:12:59.214 TTR mutations.

NOTE Confidence: 0.99543816

00:12:59.675 --> 00:13:00.875 So they actually lead to

NOTE Confidence: 0.99543816

00:13:00.875 --> 00:13:01.855 delayed onset,

NOTE Confidence: 0.9782568

00:13:02.250 --> 00:13:04.270 lower penetrance, and milder phenotype.

NOTE Confidence: 0.9905595

00:13:04.650 --> 00:13:05.950 And we think this happens

NOTE Confidence: 0.9905595

00:13:06.010 --> 00:13:07.870 because of increased tetramer stability

NOTE Confidence: 0.9905595

00:13:08.090 --> 00:13:10.190 and also slower monomer misfolding.

NOTE Confidence: 0.93494815

00:13:10.650 --> 00:13:12.250 And the clinical relevance of

NOTE Confidence: 0.93494815

00:13:12.250 --> 00:13:14.090 this is, one, typically in

NOTE Confidence: 0.93494815

00:13:14.090 --> 00:13:16.250 compound heterozygous, say, for example,

NOTE Confidence: 0.93494815

00:13:16.250 --> 00:13:17.550 like a val thirty MET

NOTE Confidence: 0.93494815

00:13:17.770 --> 00:13:19.505 with three anine one nineteen

NOTE Confidence: 0.93494815

00:13:19.505 --> 00:13:21.684 MET, those people actually have

NOTE Confidence: 0.93494815

00:13:21.825 --> 00:13:24.144 less frequent surveillance. And, also,

NOTE Confidence: 0.93494815

00:13:24.144 --> 00:13:25.425 this is relevant in terms

NOTE Confidence: 0.93494815

00:13:25.425 --> 00:13:27.105 of therapeutics. So, for example,

NOTE Confidence: 0.93494815

00:13:27.105 --> 00:13:28.485 one of the TTR stabilizers,

NOTE Confidence: 0.93494815

00:13:28.704 --> 00:13:29.204 Akaramidus,

NOTE Confidence: 0.99743456

00:13:29.665 --> 00:13:31.584 was actually based on these

NOTE Confidence: 0.99743456

00:13:31.584 --> 00:13:32.084 variants.

NOTE Confidence: 0.9964124

00:13:34.309 --> 00:13:35.990 And so with that, now

NOTE Confidence: 0.9964124

00:13:35.990 --> 00:13:38.010 that we have an abnormal

NOTE Confidence: 0.9913775

00:13:38.390 --> 00:13:39.429 like, now that we have

NOTE Confidence: 0.9913775

00:13:39.429 --> 00:13:41.429 a mutation, how does a

NOTE Confidence: 0.9913775

00:13:41.429 --> 00:13:43.670 single amino acid substitution cause

NOTE Confidence: 0.9913775

00:13:43.670 --> 00:13:45.290 such a different clinical syndrome?

NOTE Confidence: 0.97773606

00:13:45.915 --> 00:13:47.195 Well, it all comes down

NOTE Confidence: 0.97773606

00:13:47.195 --> 00:13:48.635 to how these mutations affect

NOTE Confidence: 0.97773606

00:13:48.635 --> 00:13:51.195 transthyretin stability and folding. So

NOTE Confidence: 0.97773606

00:13:51.195 --> 00:13:53.115 transthyretin, the protein, which is

NOTE Confidence: 0.97773606

00:13:53.115 --> 00:13:54.975 also known as pre albumin,

NOTE Confidence: 0.97773606

00:13:55.195 --> 00:13:56.714 is predominantly produced in the

NOTE Confidence: 0.97773606

00:13:56.714 --> 00:13:57.834 liver, but also in the

NOTE Confidence: 0.97773606

00:13:57.834 --> 00:13:59.355 choroid plexus and the retinal

NOTE Confidence: 0.97773606

00:13:59.355 --> 00:14:00.255 pigment epithelium.

NOTE Confidence: 0.95083284

00:14:02.529 --> 00:14:04.630 And under normal condition, TTR

NOTE Confidence: 0.95083284

00:14:04.769 --> 00:14:06.290 circulates as a tetramer, and

NOTE Confidence: 0.95083284

00:14:06.290 --> 00:14:08.290 it transports thyroxine and retinal

NOTE Confidence: 0.95083284

00:14:08.290 --> 00:14:09.190 binding protein.

NOTE Confidence: 0.9968449

00:14:09.570 --> 00:14:11.089 But in both wild type

NOTE Confidence: 0.9968449

00:14:11.089 --> 00:14:13.029 and variant forms, the instability

NOTE Confidence: 0.9968449

00:14:13.089 --> 00:14:14.450 of the tetramer leads to

NOTE Confidence: 0.9968449

00:14:14.450 --> 00:14:16.309 misfolding through two major mechanisms.

NOTE Confidence: 0.9725424

00:14:16.775 --> 00:14:18.295 The first mechanism is the

NOTE Confidence: 0.9725424

00:14:18.295 --> 00:14:20.315 dissociation pathway where the tetramer

NOTE Confidence: 0.9725424

00:14:20.375 --> 00:14:21.815 becomes a dimer, the dimer

NOTE Confidence: 0.9725424

00:14:21.815 --> 00:14:23.495 a monomer, and then eventually

NOTE Confidence: 0.9725424

00:14:23.495 --> 00:14:24.795 a misfolded amyloidogenic

NOTE Confidence: 0.9873416

00:14:25.255 --> 00:14:25.755 monomers

NOTE Confidence: 0.9644464

00:14:26.215 --> 00:14:27.895 that cause these amyloid tapirals

NOTE Confidence: 0.9644464

00:14:27.895 --> 00:14:28.615 that we see on the

NOTE Confidence: 0.9644464

00:14:28.615 --> 00:14:29.115 right.

NOTE Confidence: 0.9653105

00:14:29.460 --> 00:14:30.660 And then the other pathway

NOTE Confidence: 0.9653105

00:14:30.660 --> 00:14:31.480 is the proteolytic

NOTE Confidence: 0.9540865

00:14:31.860 --> 00:14:34.340 cleavage pathway where TTR undergoes

NOTE Confidence: 0.9540865

00:14:34.340 --> 00:14:36.200 a partial cleavage producing truncated

NOTE Confidence: 0.9540865

00:14:36.260 --> 00:14:37.800 fragments that are highly amyloidogenic.

NOTE Confidence: 0.9915412

00:14:38.660 --> 00:14:39.960 And in both these cases,

NOTE Confidence: 0.9915412

00:14:40.020 --> 00:14:41.160 the amyloid fibrils

NOTE Confidence: 0.99629235

00:14:41.620 --> 00:14:42.840 deposit inside

NOTE Confidence: 0.9988073

00:14:43.300 --> 00:14:44.040 the myocardium

NOTE Confidence: 0.9864343

00:14:45.105 --> 00:14:46.145 and cause what we know

NOTE Confidence: 0.9864343

00:14:46.145 --> 00:14:46.964 as frank

NOTE Confidence: 0.99275964

00:14:47.265 --> 00:14:48.084 cardiac amyloidosis.

NOTE Confidence: 0.9789532

00:14:48.705 --> 00:14:49.825 And it is important to

NOTE Confidence: 0.9789532

00:14:49.825 --> 00:14:51.185 know that while sometimes on

NOTE Confidence: 0.9789532

00:14:51.185 --> 00:14:52.625 echo for patients of suspected

NOTE Confidence: 0.9789532

00:14:52.625 --> 00:14:53.825 cardiac amyloid, we use the

NOTE Confidence: 0.9789532

00:14:53.825 --> 00:14:55.365 word mild concentric hypertrophy.

NOTE Confidence: 0.997591

00:14:55.904 --> 00:14:57.345 The myocytes are really not

NOTE Confidence: 0.997591

00:14:57.345 --> 00:14:58.945 hypertrophied. In fact, the amyloid

NOTE Confidence: 0.997591

00:14:58.945 --> 00:15:00.404 is in between the myocytes.

NOTE Confidence: 0.98584956

00:15:00.839 --> 00:15:01.800 And then the second thing

NOTE Confidence: 0.98584956

00:15:01.800 --> 00:15:03.240 that I should highlight is

NOTE Confidence: 0.98584956

00:15:03.240 --> 00:15:04.199 something that we call the

NOTE Confidence: 0.98584956

00:15:04.199 --> 00:15:06.360 seeding phenotype where amyloid begets

NOTE Confidence: 0.98584956

00:15:06.360 --> 00:15:08.120 amyloid. So, ideally, in order

NOTE Confidence: 0.98584956

00:15:08.120 --> 00:15:09.800 to prevent amyloidosis, you wanna

NOTE Confidence: 0.98584956

00:15:09.800 --> 00:15:11.560 prevent it from depositing first

NOTE Confidence: 0.98584956

00:15:11.560 --> 00:15:12.920 because the more amyloid you

NOTE Confidence: 0.98584956

00:15:12.920 --> 00:15:14.120 have, the more amyloid is

NOTE Confidence: 0.98584956

00:15:14.120 --> 00:15:15.100 gonna build up.

NOTE Confidence: 0.9940534

00:15:16.395 --> 00:15:17.355 And in terms of the

NOTE Confidence: 0.9940534

00:15:17.355 --> 00:15:19.275 natural history and as I

NOTE Confidence: 0.9940534

00:15:19.275 --> 00:15:19.775 mentioned,

NOTE Confidence: 0.98480284

00:15:20.475 --> 00:15:21.515 there are two types of

NOTE Confidence: 0.98480284

00:15:21.515 --> 00:15:22.875 cardiac amyloid, both the wild

NOTE Confidence: 0.98480284

00:15:22.875 --> 00:15:24.075 type and the inherited. But

NOTE Confidence: 0.98480284

00:15:24.075 --> 00:15:25.275 for the purposes of this

NOTE Confidence: 0.98480284

00:15:25.275 --> 00:15:27.195 talk, we're gonna predominantly focus

NOTE Confidence: 0.98480284

00:15:27.195 --> 00:15:28.335 on inherited cardiomyopathy.

NOTE Confidence: 0.95151067

00:15:29.060 --> 00:15:30.820 And, usually, these patients, for

NOTE Confidence: 0.95151067

00:15:30.820 --> 00:15:32.120 some time, are asymptomatic

NOTE Confidence: 0.94353586

00:15:32.500 --> 00:15:34.260 carriers until at some point

NOTE Confidence: 0.94353586

00:15:34.260 --> 00:15:35.540 develop what we call early

NOTE Confidence: 0.94353586

00:15:35.540 --> 00:15:37.699 stage hereditary cardiac amyloidosis where

NOTE Confidence: 0.94353586

00:15:37.699 --> 00:15:38.899 we start seeing evidence of

NOTE Confidence: 0.94353586

00:15:38.899 --> 00:15:39.959 decline in GFR,

NOTE Confidence: 0.8559684

00:15:40.420 --> 00:15:41.860 increase in their NT proBNP

NOTE Confidence: 0.8559684

00:15:41.860 --> 00:15:42.519 and troponin.

NOTE Confidence: 0.99614984

00:15:43.115 --> 00:15:44.555 And after that, we start

NOTE Confidence: 0.99614984

00:15:44.555 --> 00:15:46.475 seeing more increased heart failure

NOTE Confidence: 0.99614984

00:15:46.475 --> 00:15:46.975 hospitalizations

NOTE Confidence: 0.8760074

00:15:47.355 --> 00:15:48.735 and eventually death.

NOTE Confidence: 0.9951843

00:15:49.115 --> 00:15:50.315 But what I wanna point

NOTE Confidence: 0.9951843

00:15:50.315 --> 00:15:51.774 out is in this asymptomatic

NOTE Confidence: 0.94147235

00:15:52.235 --> 00:15:54.394 carrier stage, when the patients

NOTE Confidence: 0.94147235

00:15:54.394 --> 00:15:55.995 actually have disease and how

NOTE Confidence: 0.94147235

00:15:55.995 --> 00:15:57.214 can we predict that?

NOTE Confidence: 0.9889555

00:15:57.900 --> 00:15:59.260 And so there's the concept

NOTE Confidence: 0.9889555

00:15:59.260 --> 00:16:00.960 of predicted age of disease

NOTE Confidence: 0.96974957

00:16:01.340 --> 00:16:02.940 onset in patients with a

NOTE Confidence: 0.96974957

00:16:02.940 --> 00:16:04.000 TTR variant.

NOTE Confidence: 0.9632563

00:16:04.380 --> 00:16:06.140 And that stage moving from

NOTE Confidence: 0.9632563

00:16:06.140 --> 00:16:08.460 asymptomatic TTR variant carrier to

NOTE Confidence: 0.9632563

00:16:08.460 --> 00:16:09.440 at risk asymptomatic

NOTE Confidence: 0.9821664

00:16:09.740 --> 00:16:11.645 TTR variant is really crucial

NOTE Confidence: 0.9821664

00:16:11.945 --> 00:16:13.625 because it will influence a

NOTE Confidence: 0.9821664

00:16:13.625 --> 00:16:15.705 personalized surveillance strategy for these

NOTE Confidence: 0.9821664

00:16:15.705 --> 00:16:16.525 gene carriers.

NOTE Confidence: 0.9803096

00:16:16.985 --> 00:16:18.745 And this is predominantly affected

NOTE Confidence: 0.9803096

00:16:18.745 --> 00:16:20.665 by the specific TTR variant

NOTE Confidence: 0.9803096

00:16:20.665 --> 00:16:22.265 that they have, the typical

NOTE Confidence: 0.9803096

00:16:22.265 --> 00:16:23.725 age of onset the CTR

NOTE Confidence: 0.9690023

00:16:24.040 --> 00:16:25.500 variants have in populations,

NOTE Confidence: 0.98013824

00:16:26.040 --> 00:16:27.560 and also the age of

NOTE Confidence: 0.98013824

00:16:27.560 --> 00:16:29.720 onset in family members who

NOTE Confidence: 0.98013824

00:16:29.720 --> 00:16:30.700 have this mutation.

NOTE Confidence: 0.9861146

00:16:34.040 --> 00:16:35.320 So to shift gears back

NOTE Confidence: 0.9861146

00:16:35.320 --> 00:16:36.764 to our patient, she's in

NOTE Confidence: 0.9861146

00:16:36.764 --> 00:16:38.704 clinic. You're taking your history.

NOTE Confidence: 0.9861146

00:16:39.004 --> 00:16:39.964 She tells you, well, I

NOTE Confidence: 0.9861146

00:16:39.964 --> 00:16:40.925 have a history of high

NOTE Confidence: 0.9861146

00:16:40.925 --> 00:16:41.964 blood pressure. I'm on three

NOTE Confidence: 0.9861146

00:16:41.964 --> 00:16:42.944 blood pressure medications.

NOTE Confidence: 0.99491155

00:16:43.725 --> 00:16:45.165 She has obesity with a

NOTE Confidence: 0.99491155

00:16:45.165 --> 00:16:47.185 BMI of thirty five, bilateral

NOTE Confidence: 0.99491155

00:16:47.324 --> 00:16:48.845 carpal tunnel syndrome, and lumbar

NOTE Confidence: 0.99491155

00:16:48.845 --> 00:16:49.745 spinal stenosis.

NOTE Confidence: 0.99880284

00:16:50.100 --> 00:16:51.139 She's had a history of

NOTE Confidence: 0.99880284

00:16:51.139 --> 00:16:52.839 bilateral carpal tunnel release

NOTE Confidence: 0.9784253

00:16:53.220 --> 00:16:54.579 as well as fixation of

NOTE Confidence: 0.9784253

00:16:54.579 --> 00:16:55.480 lumbar stenosis.

NOTE Confidence: 0.9875229

00:16:55.940 --> 00:16:57.459 She has extensive family history

NOTE Confidence: 0.9875229

00:16:57.459 --> 00:16:59.300 of hypertrophic cardiomyopathy, which we'll

NOTE Confidence: 0.9875229

00:16:59.300 --> 00:17:00.759 delve into in a second,

NOTE Confidence: 0.99574614

00:17:01.620 --> 00:17:03.160 and really has unremarkable

NOTE Confidence: 0.9993395

00:17:03.620 --> 00:17:04.919 social risk factors

NOTE Confidence: 0.9360644

00:17:05.265 --> 00:17:06.244 and really nonrelevant

NOTE Confidence: 0.999174

00:17:06.705 --> 00:17:07.205 allergies.

NOTE Confidence: 0.9912894

00:17:08.705 --> 00:17:10.305 And in terms of her

NOTE Confidence: 0.9912894

00:17:10.305 --> 00:17:11.505 family history, this is a

NOTE Confidence: 0.9912894

00:17:11.505 --> 00:17:12.625 pedigree that I was able

NOTE Confidence: 0.9912894

00:17:12.625 --> 00:17:14.165 to compile from the chart.

NOTE Confidence: 0.9912894

00:17:14.305 --> 00:17:15.445 So our proband,

NOTE Confidence: 0.99447054

00:17:16.065 --> 00:17:17.505 let me just use the

NOTE Confidence: 0.99447054

00:17:17.505 --> 00:17:18.005 pointer.

NOTE Confidence: 0.93714863

00:17:18.590 --> 00:17:20.030 Our Proband, who is right

NOTE Confidence: 0.93714863

00:17:20.030 --> 00:17:21.390 here, she is a carrier

NOTE Confidence: 0.93714863

00:17:21.390 --> 00:17:22.290 of this variant,

NOTE Confidence: 0.99342906

00:17:22.750 --> 00:17:24.990 basically came after her son

NOTE Confidence: 0.99342906

00:17:24.990 --> 00:17:25.810 was diagnosed,

NOTE Confidence: 0.9906227

00:17:26.430 --> 00:17:28.510 of HCM in at a

NOTE Confidence: 0.9906227

00:17:28.510 --> 00:17:29.950 young age and then went

NOTE Confidence: 0.9906227

00:17:29.950 --> 00:17:31.230 to ultimately receive a heart

NOTE Confidence: 0.9906227

00:17:31.230 --> 00:17:32.510 transplant here at Yale at

NOTE Confidence: 0.9906227

00:17:32.510 --> 00:17:33.490 the age of forty.

NOTE Confidence: 0.999039

00:17:33.825 --> 00:17:35.024 He was tested and was

NOTE Confidence: 0.999039

00:17:35.024 --> 00:17:36.085 found to have

NOTE Confidence: 0.88918763

00:17:36.385 --> 00:17:37.764 a sarcomereic mutation,

NOTE Confidence: 0.98485357

00:17:38.385 --> 00:17:39.984 and his son also was

NOTE Confidence: 0.98485357

00:17:39.984 --> 00:17:41.345 diagnosed with HCM at two

NOTE Confidence: 0.98485357

00:17:41.345 --> 00:17:42.784 months and had sudden cardiac

NOTE Confidence: 0.98485357

00:17:42.784 --> 00:17:44.144 death at ten years and

NOTE Confidence: 0.98485357

00:17:44.144 --> 00:17:45.744 eventually also went to have

NOTE Confidence: 0.98485357

00:17:45.744 --> 00:17:46.565 a heart transplant

NOTE Confidence: 0.9851687

00:17:46.865 --> 00:17:48.085 at fourteen year old.

NOTE Confidence: 0.99711996

00:17:48.580 --> 00:17:50.180 Now in terms of our

NOTE Confidence: 0.99711996

00:17:50.180 --> 00:17:51.880 patient's maternal history,

NOTE Confidence: 0.9982414

00:17:52.260 --> 00:17:53.220 we know that she has

NOTE Confidence: 0.9982414

00:17:53.220 --> 00:17:55.160 this unclear history of cardiomyopathy

NOTE Confidence: 0.9570933

00:17:56.100 --> 00:17:57.300 in both her mom and

NOTE Confidence: 0.9570933

00:17:57.300 --> 00:17:59.160 her maternal aunt, but really

NOTE Confidence: 0.9570933

00:17:59.220 --> 00:18:01.160 unclear what's going on there.

NOTE Confidence: 0.9570933

00:18:01.345 --> 00:18:02.625 And then the father here

NOTE Confidence: 0.9570933

00:18:02.625 --> 00:18:04.145 has an extensive family history

NOTE Confidence: 0.9570933

00:18:04.145 --> 00:18:05.925 of HCM and we think

NOTE Confidence: 0.9958041

00:18:06.225 --> 00:18:07.745 sent the HCM gene down

NOTE Confidence: 0.9958041

00:18:07.745 --> 00:18:09.425 to his sons. Her daughter

NOTE Confidence: 0.9958041

00:18:09.425 --> 00:18:10.785 and her granddaughter were both

NOTE Confidence: 0.9958041

00:18:10.785 --> 00:18:11.605 free of disease.

NOTE Confidence: 0.9981164

00:18:13.660 --> 00:18:15.180 On exam, her vital signs

NOTE Confidence: 0.9981164

00:18:15.180 --> 00:18:16.480 are pretty much unremarkable.

NOTE Confidence: 0.9989475

00:18:17.660 --> 00:18:19.040 Her exam is also

NOTE Confidence: 0.9969134

00:18:19.420 --> 00:18:21.020 unremarkable with no signs or

NOTE Confidence: 0.9969134

00:18:21.020 --> 00:18:22.320 symptoms of heart failure

NOTE Confidence: 0.9815359

00:18:22.619 --> 00:18:24.220 and no evidence of any,

NOTE Confidence: 0.9815359

00:18:24.540 --> 00:18:25.040 pathognomonic,

NOTE Confidence: 0.99992895

00:18:25.980 --> 00:18:26.480 amyloidosis

NOTE Confidence: 0.99812365

00:18:26.940 --> 00:18:27.440 signs.

NOTE Confidence: 0.9934303

00:18:28.715 --> 00:18:29.915 So what do the guidelines

NOTE Confidence: 0.9934303

00:18:29.915 --> 00:18:31.195 tell us? You know, how

NOTE Confidence: 0.9934303

00:18:31.195 --> 00:18:32.475 are we gonna proceed to

NOTE Confidence: 0.9934303

00:18:32.475 --> 00:18:34.315 diagnosing her with so called

NOTE Confidence: 0.9934303

00:18:34.315 --> 00:18:35.215 cardiac amyloidosis?

NOTE Confidence: 0.9637057

00:18:35.675 --> 00:18:37.355 Well, first, we're gonna go

NOTE Confidence: 0.9637057

00:18:37.355 --> 00:18:38.955 ahead and get our history,

NOTE Confidence: 0.9637057

00:18:38.955 --> 00:18:40.395 our EKG, our echo, and

NOTE Confidence: 0.9637057

00:18:40.395 --> 00:18:42.040 our cardiac MRI. We're gonna

NOTE Confidence: 0.9637057

00:18:42.040 --> 00:18:43.320 make sure she has no

NOTE Confidence: 0.9637057

00:18:43.320 --> 00:18:45.080 AL amyloid doses based on

NOTE Confidence: 0.9637057

00:18:45.080 --> 00:18:46.220 SBAP with immunofixation

NOTE Confidence: 0.95754653

00:18:47.000 --> 00:18:48.619 and serum free light chains,

NOTE Confidence: 0.96730006

00:18:49.400 --> 00:18:50.440 and that's kind of the

NOTE Confidence: 0.96730006

00:18:50.440 --> 00:18:51.880 pathway over here, which is

NOTE Confidence: 0.96730006

00:18:51.880 --> 00:18:52.840 not the focus of our

NOTE Confidence: 0.96730006

00:18:52.840 --> 00:18:54.055 talk. And if all of

NOTE Confidence: 0.96730006

00:18:54.055 --> 00:18:55.734 this workup is negative for

NOTE Confidence: 0.96730006

00:18:55.734 --> 00:18:57.575 AL amyloidosis, then we're gonna

NOTE Confidence: 0.96730006

00:18:57.575 --> 00:18:59.435 proceed to get a PYP

NOTE Confidence: 0.96730006

00:18:59.494 --> 00:19:01.515 or HDMP or any other

NOTE Confidence: 0.96730006

00:19:01.655 --> 00:19:04.234 cardio cardiac radionuclide imaging.

NOTE Confidence: 0.9937311

00:19:04.535 --> 00:19:05.835 And if that is negative,

NOTE Confidence: 0.9937311

00:19:06.055 --> 00:19:07.530 then by the guidelines, this

NOTE Confidence: 0.9937311

00:19:07.530 --> 00:19:08.970 is unlikely to have cardiac

NOTE Confidence: 0.9937311

00:19:08.970 --> 00:19:10.670 amyloid. And if it's positive,

NOTE Confidence: 0.9937311

00:19:10.730 --> 00:19:12.170 then we proceed to genetic

NOTE Confidence: 0.9937311

00:19:12.170 --> 00:19:12.670 testing.

NOTE Confidence: 0.950152

00:19:13.850 --> 00:19:15.130 And this is exactly what

NOTE Confidence: 0.950152

00:19:15.130 --> 00:19:16.810 we did. Her labs were

NOTE Confidence: 0.950152

00:19:16.810 --> 00:19:18.090 pretty unremarkable, so n t

NOTE Confidence: 0.950152

00:19:18.090 --> 00:19:19.875 proBNP was below assay. High

NOTE Confidence: 0.950152

00:19:19.955 --> 00:19:22.135 High sensitivity troponin, very unlikely,

NOTE Confidence: 0.950152

00:19:22.195 --> 00:19:24.035 but really is nine. Pre

NOTE Confidence: 0.950152

00:19:24.035 --> 00:19:25.555 albumin, which is again the

NOTE Confidence: 0.950152

00:19:25.555 --> 00:19:26.835 t t r, is seventeen

NOTE Confidence: 0.950152

00:19:26.835 --> 00:19:27.875 point eight. She had a

NOTE Confidence: 0.950152

00:19:27.875 --> 00:19:29.795 normal creatinine, and her AL

NOTE Confidence: 0.950152

00:19:29.795 --> 00:19:30.855 labs were normal.

NOTE Confidence: 0.9384546

00:19:32.050 --> 00:19:33.590 She also had an EKG

NOTE Confidence: 0.9384546

00:19:33.730 --> 00:19:35.250 which showed sinus rhythm with

NOTE Confidence: 0.9384546

00:19:35.250 --> 00:19:36.710 a prolonged PR interval

NOTE Confidence: 0.99400026

00:19:37.170 --> 00:19:39.090 and a borderline left axis

NOTE Confidence: 0.99400026

00:19:39.090 --> 00:19:39.590 deviation.

NOTE Confidence: 0.9973907

00:19:41.170 --> 00:19:42.230 She had an echocardiogram

NOTE Confidence: 0.957338

00:19:43.330 --> 00:19:45.810 which showed, again, increased LV

NOTE Confidence: 0.957338

00:19:45.810 --> 00:19:47.425 wall thickness with an estimated

NOTE Confidence: 0.957338

00:19:47.425 --> 00:19:47.925 interventricular

NOTE Confidence: 0.9988452

00:19:48.305 --> 00:19:49.825 septum thickness of about one

NOTE Confidence: 0.9988452

00:19:49.825 --> 00:19:50.805 point two centimeters.

NOTE Confidence: 0.9978371

00:19:52.225 --> 00:19:52.965 She had

NOTE Confidence: 0.98148364

00:19:53.345 --> 00:19:55.185 normal preserved left ventricular and

NOTE Confidence: 0.98148364

00:19:55.185 --> 00:19:57.345 right ventricular systolic function, some

NOTE Confidence: 0.98148364

00:19:57.345 --> 00:19:58.165 mild MR,

NOTE Confidence: 0.95841056

00:19:58.545 --> 00:20:00.705 but really nothing otherwise significant

NOTE Confidence: 0.95841056

00:20:00.705 --> 00:20:02.244 and no pericardial effusion.

NOTE Confidence: 0.9923862

00:20:03.080 --> 00:20:04.600 Strain was not performed on

NOTE Confidence: 0.9923862

00:20:04.600 --> 00:20:06.060 the echo, and this was

NOTE Confidence: 0.9923862

00:20:06.119 --> 00:20:07.660 performed at an outside hospital.

NOTE Confidence: 0.9819963

00:20:09.320 --> 00:20:10.460 She also had,

NOTE Confidence: 0.9041946

00:20:11.000 --> 00:20:12.520 a technician ninety nine m

NOTE Confidence: 0.9041946

00:20:12.520 --> 00:20:13.020 HMDP

NOTE Confidence: 0.994982

00:20:13.400 --> 00:20:13.900 study,

NOTE Confidence: 0.99819416

00:20:14.600 --> 00:20:15.580 which was negative.

NOTE Confidence: 0.9995172

00:20:16.215 --> 00:20:16.715 Basically,

NOTE Confidence: 0.9747743

00:20:17.414 --> 00:20:18.695 the visual or the three

NOTE Confidence: 0.9747743

00:20:18.695 --> 00:20:20.294 hour visual uptake score was

NOTE Confidence: 0.9747743

00:20:20.294 --> 00:20:21.255 zero. As you can see

NOTE Confidence: 0.9747743

00:20:21.255 --> 00:20:23.095 here, there's no heart on

NOTE Confidence: 0.9747743

00:20:23.095 --> 00:20:23.595 the

NOTE Confidence: 0.8133583

00:20:23.895 --> 00:20:24.395 red.

NOTE Confidence: 0.97860086

00:20:25.655 --> 00:20:26.855 And she had a nuclear

NOTE Confidence: 0.97860086

00:20:26.855 --> 00:20:28.294 SPECT as well, which was

NOTE Confidence: 0.97860086

00:20:28.294 --> 00:20:29.920 negative. And the way I

NOTE Confidence: 0.97860086

00:20:29.920 --> 00:20:31.040 see this for people who

NOTE Confidence: 0.97860086

00:20:31.040 --> 00:20:31.920 don't look at this a

NOTE Confidence: 0.97860086

00:20:31.920 --> 00:20:32.960 lot, if you see a

NOTE Confidence: 0.97860086

00:20:32.960 --> 00:20:34.320 heart, it's a bad thing.

NOTE Confidence: 0.97860086

00:20:34.320 --> 00:20:35.280 If you don't see a

NOTE Confidence: 0.97860086

00:20:35.280 --> 00:20:36.560 heart, it's a good thing.

NOTE Confidence: 0.97860086

00:20:36.560 --> 00:20:37.520 And the fact that we

NOTE Confidence: 0.97860086

00:20:37.520 --> 00:20:38.640 don't see a heart means

NOTE Confidence: 0.97860086

00:20:38.640 --> 00:20:39.860 that there was no myocardial

NOTE Confidence: 0.97860086

00:20:39.920 --> 00:20:40.420 uptake.

NOTE Confidence: 0.99876326

00:20:42.015 --> 00:20:43.215 She also had a cardiac

NOTE Confidence: 0.99876326

00:20:43.215 --> 00:20:43.715 MRI,

NOTE Confidence: 0.9761504

00:20:45.295 --> 00:20:47.635 which basically was read as

NOTE Confidence: 0.9761504

00:20:47.695 --> 00:20:49.395 no evidence of cardiac amyloidosis.

NOTE Confidence: 0.9761504

00:20:49.615 --> 00:20:51.215 She had normal right right

NOTE Confidence: 0.9761504

00:20:51.215 --> 00:20:52.734 and left ventricular size and

NOTE Confidence: 0.9761504

00:20:52.734 --> 00:20:54.175 function. She had no left

NOTE Confidence: 0.9761504

00:20:54.175 --> 00:20:57.139 ventricular gadolinium enhancement, and the

NOTE Confidence: 0.9761504

00:20:57.139 --> 00:20:58.580 images are on this bottom

NOTE Confidence: 0.9761504

00:20:58.580 --> 00:20:59.539 right side. This is one

NOTE Confidence: 0.9761504

00:20:59.539 --> 00:21:00.039 representative

NOTE Confidence: 0.9986985

00:21:00.340 --> 00:21:00.840 image.

NOTE Confidence: 0.93573725

00:21:01.299 --> 00:21:02.179 This is a t one

NOTE Confidence: 0.93573725

00:21:02.179 --> 00:21:03.940 scout images which basically showed

NOTE Confidence: 0.93573725

00:21:03.940 --> 00:21:05.619 a normal, quote, unquote, nulling

NOTE Confidence: 0.93573725

00:21:05.619 --> 00:21:06.820 pattern. She had mild by

NOTE Confidence: 0.93573725

00:21:06.820 --> 00:21:08.820 atrial enlargement, normal t maps,

NOTE Confidence: 0.93573725

00:21:08.820 --> 00:21:10.019 and the ECV was not

NOTE Confidence: 0.93573725

00:21:10.019 --> 00:21:10.519 described.

NOTE Confidence: 0.9983551

00:21:12.415 --> 00:21:13.875 So let's put her together.

NOTE Confidence: 0.9833579

00:21:14.255 --> 00:21:15.375 This is a sixty eight

NOTE Confidence: 0.9833579

00:21:15.375 --> 00:21:16.655 year old woman with a

NOTE Confidence: 0.9833579

00:21:16.655 --> 00:21:18.035 val one twenty two isoleucine

NOTE Confidence: 0.9833579

00:21:18.255 --> 00:21:20.095 TTR variant and no clinical

NOTE Confidence: 0.9833579

00:21:20.095 --> 00:21:22.175 evidence of infiltrative cardiac disease

NOTE Confidence: 0.9833579

00:21:22.175 --> 00:21:23.535 based on lab and imaging

NOTE Confidence: 0.9833579

00:21:23.535 --> 00:21:24.975 data. And I know some

NOTE Confidence: 0.9833579

00:21:24.975 --> 00:21:26.355 of you may bring up

NOTE Confidence: 0.98923033

00:21:26.710 --> 00:21:28.230 the increased LV wall thickness,

NOTE Confidence: 0.98923033

00:21:28.230 --> 00:21:29.690 but she was also hypertensive

NOTE Confidence: 0.98923033

00:21:29.990 --> 00:21:31.610 on three blood pressure medications

NOTE Confidence: 0.98923033

00:21:31.750 --> 00:21:32.250 with

NOTE Confidence: 0.79485303

00:21:32.869 --> 00:21:33.770 normal imaging.

NOTE Confidence: 0.9557018

00:21:34.070 --> 00:21:35.690 And so, she was defined

NOTE Confidence: 0.9557018

00:21:35.830 --> 00:21:37.210 as a patient with preclinical

NOTE Confidence: 0.9557018

00:21:37.430 --> 00:21:37.930 disease.

NOTE Confidence: 0.9455051

00:21:39.705 --> 00:21:41.385 So let's look at our

NOTE Confidence: 0.9455051

00:21:41.385 --> 00:21:43.725 diagnostic tests of ATTR amyloidosis

NOTE Confidence: 0.9455051

00:21:43.945 --> 00:21:45.244 and how are we doing.

NOTE Confidence: 0.9455051

00:21:45.465 --> 00:21:46.984 Well, echo, great. It's loose

NOTE Confidence: 0.9455051

00:21:46.984 --> 00:21:49.065 for diagnostics and sometimes also

NOTE Confidence: 0.9455051

00:21:49.065 --> 00:21:50.445 for therapeutic surveillance.

NOTE Confidence: 0.98424923

00:21:51.145 --> 00:21:52.424 We mostly care about the

NOTE Confidence: 0.98424923

00:21:52.424 --> 00:21:54.409 global longitudinal strain, the wall

NOTE Confidence: 0.98424923

00:21:54.409 --> 00:21:56.109 thickness, the diastolic function.

NOTE Confidence: 0.995308

00:21:56.890 --> 00:21:57.549 We also

NOTE Confidence: 0.93974155

00:21:57.929 --> 00:21:59.770 are happy because it's widely

NOTE Confidence: 0.93974155

00:21:59.770 --> 00:22:01.609 available with no ionizing radiation

NOTE Confidence: 0.93974155

00:22:01.609 --> 00:22:03.150 and pretty rather short duration.

NOTE Confidence: 0.93974155

00:22:03.450 --> 00:22:05.049 But the principal limitation are

NOTE Confidence: 0.93974155

00:22:05.049 --> 00:22:06.490 mostly body habitus of the

NOTE Confidence: 0.93974155

00:22:06.490 --> 00:22:08.375 patient, limited tissue characterization,

NOTE Confidence: 0.9857486

00:22:08.915 --> 00:22:10.135 and it's really nonspecific

NOTE Confidence: 0.99759406

00:22:10.435 --> 00:22:12.195 in determining amyloid from anything

NOTE Confidence: 0.99759406

00:22:12.195 --> 00:22:12.695 else.

NOTE Confidence: 0.99891025

00:22:13.315 --> 00:22:14.535 In terms of CMR,

NOTE Confidence: 0.9892755

00:22:15.155 --> 00:22:16.994 it's really mostly used for

NOTE Confidence: 0.9892755

00:22:16.994 --> 00:22:17.494 prognostic,

NOTE Confidence: 0.93126345

00:22:19.669 --> 00:22:21.289 from a prognostic importance.

NOTE Confidence: 0.97596496

00:22:21.750 --> 00:22:22.789 Usually, we look at the

NOTE Confidence: 0.97596496

00:22:22.789 --> 00:22:24.470 late gadolinium enhancement pattern, the

NOTE Confidence: 0.97596496

00:22:24.470 --> 00:22:26.169 nulling pattern, the extracellular

NOTE Confidence: 0.9217027

00:22:26.470 --> 00:22:27.830 volume fraction, and the native

NOTE Confidence: 0.9217027

00:22:27.830 --> 00:22:29.750 myocardial t one time. It

NOTE Confidence: 0.9217027

00:22:29.750 --> 00:22:30.409 is also,

NOTE Confidence: 0.9838029

00:22:31.590 --> 00:22:33.369 offered with no ionizing radiation,

NOTE Confidence: 0.9849264

00:22:34.215 --> 00:22:35.494 the function and the tissue

NOTE Confidence: 0.9849264

00:22:35.494 --> 00:22:37.174 characterization and grade, and it

NOTE Confidence: 0.9849264

00:22:37.174 --> 00:22:38.875 does exclude alternative etiologies.

NOTE Confidence: 0.96292603

00:22:39.335 --> 00:22:40.535 But it does need center

NOTE Confidence: 0.96292603

00:22:40.535 --> 00:22:42.535 expertise. It's dependent on patient

NOTE Confidence: 0.96292603

00:22:42.535 --> 00:22:44.054 factors and really,

NOTE Confidence: 0.99175483

00:22:44.375 --> 00:22:45.994 does not have much multicenter

NOTE Confidence: 0.99175483

00:22:46.294 --> 00:22:47.115 study data.

NOTE Confidence: 0.9634118

00:22:47.450 --> 00:22:48.490 And finally, in terms of

NOTE Confidence: 0.9634118

00:22:48.490 --> 00:22:48.990 radionuclide

NOTE Confidence: 0.9991205

00:22:49.450 --> 00:22:49.950 imaging,

NOTE Confidence: 0.97574663

00:22:50.410 --> 00:22:51.450 we do need SPECT or

NOTE Confidence: 0.97574663

00:22:51.450 --> 00:22:52.350 SPECT CT.

NOTE Confidence: 0.9595334

00:22:53.530 --> 00:22:55.369 It excludes plasma cell disorder,

NOTE Confidence: 0.9595334

00:22:55.369 --> 00:22:56.809 and it's widely available. It

NOTE Confidence: 0.9595334

00:22:56.809 --> 00:22:58.809 has minimal radiation exposure but

NOTE Confidence: 0.9595334

00:22:58.809 --> 00:23:00.109 with long trace of incubation

NOTE Confidence: 0.9595334

00:23:00.250 --> 00:23:02.170 time and also has false

NOTE Confidence: 0.9595334

00:23:02.170 --> 00:23:03.150 positive scans.

NOTE Confidence: 0.9766748

00:23:03.494 --> 00:23:04.775 And in terms of the

NOTE Confidence: 0.9766748

00:23:04.775 --> 00:23:07.494 limitations of radionuclide imaging in

NOTE Confidence: 0.9766748

00:23:07.494 --> 00:23:09.575 cardiac amyloid per se, and

NOTE Confidence: 0.9766748

00:23:09.575 --> 00:23:10.695 while it has become a

NOTE Confidence: 0.9766748

00:23:10.695 --> 00:23:12.715 cornerstone for diagnosing tristhyridine

NOTE Confidence: 0.9915999

00:23:13.015 --> 00:23:13.915 cardiac amyloidosis,

NOTE Confidence: 0.98386306

00:23:14.615 --> 00:23:15.355 its sensitivity

NOTE Confidence: 0.98492414

00:23:15.734 --> 00:23:17.435 really depends on disease burden.

NOTE Confidence: 0.8489606

00:23:17.820 --> 00:23:19.100 So really uptake can be

NOTE Confidence: 0.8489606

00:23:19.100 --> 00:23:19.600 negative,

NOTE Confidence: 0.9146271

00:23:20.140 --> 00:23:21.899 in early stage disease. Also,

NOTE Confidence: 0.9146271

00:23:21.899 --> 00:23:23.659 certain genetic mutations like the

NOTE Confidence: 0.9146271

00:23:23.659 --> 00:23:24.960 val fifty MET and

NOTE Confidence: 0.9599813

00:23:25.260 --> 00:23:27.019 the phenyl phenyl sixty four

NOTE Confidence: 0.9599813

00:23:27.019 --> 00:23:28.940 leucine are also associated with

NOTE Confidence: 0.9599813

00:23:28.940 --> 00:23:30.299 false negatives because of a

NOTE Confidence: 0.9599813

00:23:30.299 --> 00:23:32.159 distinct amyloid fibril composition.

NOTE Confidence: 0.985033

00:23:33.085 --> 00:23:34.365 And in addition, as we've

NOTE Confidence: 0.985033

00:23:34.365 --> 00:23:35.325 learned over the past few

NOTE Confidence: 0.985033

00:23:35.325 --> 00:23:37.244 years, planar imaging alone can

NOTE Confidence: 0.985033

00:23:37.244 --> 00:23:37.744 overestimate

NOTE Confidence: 0.94872874

00:23:38.045 --> 00:23:39.485 cardiac involvement. So we do

NOTE Confidence: 0.94872874

00:23:39.485 --> 00:23:41.005 need SPECT or SPECT CT

NOTE Confidence: 0.94872874

00:23:41.005 --> 00:23:41.505 imaging.

NOTE Confidence: 0.997928

00:23:44.045 --> 00:23:45.244 And with that, you know,

NOTE Confidence: 0.997928

00:23:45.244 --> 00:23:46.145 I did ask

NOTE Confidence: 0.9699084

00:23:46.720 --> 00:23:48.640 Chachibuty and Open Evidence, our,

NOTE Confidence: 0.9699084

00:23:48.960 --> 00:23:50.560 biggest resources, to tell me

NOTE Confidence: 0.9699084

00:23:50.560 --> 00:23:51.360 what to do with this

NOTE Confidence: 0.9699084

00:23:51.360 --> 00:23:53.360 patient. And in concordance with

NOTE Confidence: 0.9699084

00:23:53.360 --> 00:23:54.960 the guidelines, they say that

NOTE Confidence: 0.9699084

00:23:54.960 --> 00:23:57.060 there's no disease modifying therapy

NOTE Confidence: 0.9699084

00:23:57.120 --> 00:23:57.620 indicated

NOTE Confidence: 0.99946195

00:23:58.320 --> 00:23:59.380 at this point.

NOTE Confidence: 0.97291505

00:23:59.914 --> 00:24:01.434 Yeah. But let me all

NOTE Confidence: 0.97291505

00:24:01.434 --> 00:24:02.794 ask you this. This is

NOTE Confidence: 0.97291505

00:24:02.794 --> 00:24:03.755 a sixty eight year old

NOTE Confidence: 0.97291505

00:24:03.755 --> 00:24:05.595 patient. She has a disease

NOTE Confidence: 0.97291505

00:24:05.595 --> 00:24:07.355 causing variant. She already has

NOTE Confidence: 0.97291505

00:24:07.355 --> 00:24:08.875 carpal tunnel and lumbar spinal

NOTE Confidence: 0.97291505

00:24:08.875 --> 00:24:10.174 stenosis and maybe

NOTE Confidence: 0.9137578

00:24:10.475 --> 00:24:12.155 increased LV wall thickness. And

NOTE Confidence: 0.9137578

00:24:12.155 --> 00:24:12.655 despite

NOTE Confidence: 0.992603

00:24:13.109 --> 00:24:15.190 negative imaging and workup, we're

NOTE Confidence: 0.992603

00:24:15.190 --> 00:24:16.730 really offering her surveillance.

NOTE Confidence: 0.9971598

00:24:17.750 --> 00:24:18.950 And I think that question

NOTE Confidence: 0.9971598

00:24:18.950 --> 00:24:20.309 just gets us to pause

NOTE Confidence: 0.9971598

00:24:20.309 --> 00:24:21.910 and really think of how

NOTE Confidence: 0.9971598

00:24:21.910 --> 00:24:24.230 we manage asymptomatic TTR variant

NOTE Confidence: 0.9971598

00:24:24.230 --> 00:24:24.730 carriers.

NOTE Confidence: 0.9979113

00:24:25.255 --> 00:24:26.934 Really, the management has been

NOTE Confidence: 0.9979113

00:24:26.934 --> 00:24:28.934 focused on defining the variant,

NOTE Confidence: 0.9979113

00:24:28.934 --> 00:24:30.075 the age of onset,

NOTE Confidence: 0.9860892

00:24:30.615 --> 00:24:31.895 really looking at the history

NOTE Confidence: 0.9860892

00:24:31.895 --> 00:24:33.335 and the physical exam and

NOTE Confidence: 0.9860892

00:24:33.335 --> 00:24:34.615 whether they have any signs

NOTE Confidence: 0.9860892

00:24:34.615 --> 00:24:36.635 and symptoms of cardiac amyloidosis,

NOTE Confidence: 0.98395

00:24:38.070 --> 00:24:40.070 directed clinical testing as a

NOTE Confidence: 0.98395

00:24:40.070 --> 00:24:41.929 baseline and also as surveillance,

NOTE Confidence: 0.99736214

00:24:42.309 --> 00:24:44.230 and then frequency based on

NOTE Confidence: 0.99736214

00:24:44.230 --> 00:24:45.750 symptoms. So we're really gonna

NOTE Confidence: 0.99736214

00:24:45.750 --> 00:24:46.869 wait for her to declare

NOTE Confidence: 0.99736214

00:24:46.869 --> 00:24:48.809 herself and then treat her.

NOTE Confidence: 0.96101284

00:24:51.195 --> 00:24:53.455 And, again, this slide summarizes

NOTE Confidence: 0.96101284

00:24:53.595 --> 00:24:55.695 how we currently assess progression.

NOTE Confidence: 0.9555639

00:24:55.994 --> 00:24:57.755 We track downstream effects. We

NOTE Confidence: 0.9555639

00:24:57.755 --> 00:24:59.994 track NT proBNP, troponin, renal

NOTE Confidence: 0.9555639

00:24:59.994 --> 00:25:01.595 function, and strain, or we

NOTE Confidence: 0.9555639

00:25:01.595 --> 00:25:03.934 quantify burden based on radionuclide

NOTE Confidence: 0.992686

00:25:04.234 --> 00:25:06.040 imaging or CMR. And I

NOTE Confidence: 0.992686

00:25:06.040 --> 00:25:07.580 wanna mention that radionuclide

NOTE Confidence: 0.9925294

00:25:07.880 --> 00:25:09.000 imaging is really not the

NOTE Confidence: 0.9925294

00:25:09.000 --> 00:25:11.180 modality to assess amyloid burden.

NOTE Confidence: 0.9722488

00:25:11.640 --> 00:25:12.920 But, again, let's reflect on

NOTE Confidence: 0.9722488

00:25:12.920 --> 00:25:15.340 this paradigm because everything here

NOTE Confidence: 0.9722488

00:25:15.480 --> 00:25:18.220 represents disease after amyloid deposited.

NOTE Confidence: 0.96774614

00:25:18.675 --> 00:25:19.715 So what if we shift

NOTE Confidence: 0.96774614

00:25:19.715 --> 00:25:20.915 our focus a little bit

NOTE Confidence: 0.96774614

00:25:20.915 --> 00:25:22.535 earlier before wall thickening,

NOTE Confidence: 0.9909863

00:25:22.915 --> 00:25:24.915 before elevated biomarkers to the

NOTE Confidence: 0.9909863

00:25:24.915 --> 00:25:25.415 asymptomatic

NOTE Confidence: 0.84644157

00:25:26.035 --> 00:25:26.535 predeposition

NOTE Confidence: 0.9754288

00:25:26.915 --> 00:25:28.835 phase where fibrils are just

NOTE Confidence: 0.9754288

00:25:28.835 --> 00:25:30.595 beginning to form? And that's

NOTE Confidence: 0.9754288

00:25:30.595 --> 00:25:31.795 exactly where the field is

NOTE Confidence: 0.9754288

00:25:31.795 --> 00:25:33.530 heading, from treating end stage

NOTE Confidence: 0.9754288

00:25:33.530 --> 00:25:34.030 manifestations

NOTE Confidence: 0.9842646

00:25:34.650 --> 00:25:36.890 to detecting and intervening during

NOTE Confidence: 0.9842646

00:25:36.890 --> 00:25:38.270 amyloid formation itself,

NOTE Confidence: 0.99794686

00:25:38.650 --> 00:25:41.130 preventing clinical disease rather than

NOTE Confidence: 0.99794686

00:25:41.130 --> 00:25:42.270 reacting to it.

NOTE Confidence: 0.97828597

00:25:43.770 --> 00:25:44.730 And this is what the

NOTE Confidence: 0.97828597

00:25:44.730 --> 00:25:46.145 next few slides will explore.

NOTE Confidence: 0.97828597

00:25:46.285 --> 00:25:47.484 We're gonna explore how blood

NOTE Confidence: 0.97828597

00:25:47.484 --> 00:25:48.385 based biomarkers,

NOTE Confidence: 0.9642437

00:25:48.925 --> 00:25:50.765 imaging, and new tracers as

NOTE Confidence: 0.9642437

00:25:50.765 --> 00:25:52.385 well as emerging AI tools

NOTE Confidence: 0.9642437

00:25:52.525 --> 00:25:53.905 may allow us to identify

NOTE Confidence: 0.9642437

00:25:54.045 --> 00:25:54.545 amyloidosis

NOTE Confidence: 0.9998074

00:25:55.005 --> 00:25:55.505 before

NOTE Confidence: 0.99644357

00:25:55.885 --> 00:25:57.825 it even declares itself clinically.

NOTE Confidence: 0.96782

00:26:00.200 --> 00:26:02.060 So let's talk about biomarkers,

NOTE Confidence: 0.99483526

00:26:02.440 --> 00:26:03.640 and this is for my,

NOTE Confidence: 0.99335647

00:26:04.520 --> 00:26:05.820 basic science fans.

NOTE Confidence: 0.8108567

00:26:07.720 --> 00:26:09.800 The first assay is measuring

NOTE Confidence: 0.8108567

00:26:09.800 --> 00:26:10.780 actual tranacyridine

NOTE Confidence: 0.9487211

00:26:11.240 --> 00:26:13.100 concentration or measuring prealbumin

NOTE Confidence: 0.9019349

00:26:13.400 --> 00:26:13.900 concentration.

NOTE Confidence: 0.9559904

00:26:14.440 --> 00:26:16.815 And this is basically uses

NOTE Confidence: 0.9559904

00:26:16.815 --> 00:26:17.555 an immunoturbidometric

NOTE Confidence: 0.9984125

00:26:18.335 --> 00:26:18.835 method

NOTE Confidence: 0.94210124

00:26:19.135 --> 00:26:20.494 where you just, you know,

NOTE Confidence: 0.94210124

00:26:20.494 --> 00:26:22.195 basically combine polyclonal

NOTE Confidence: 0.9366206

00:26:22.494 --> 00:26:24.275 antibodies with a patient's serum.

NOTE Confidence: 0.96826357

00:26:25.135 --> 00:26:27.455 Antigen antibody complexes form and

NOTE Confidence: 0.96826357

00:26:27.455 --> 00:26:29.369 it increases turbidity. And it

NOTE Confidence: 0.96826357

00:26:29.450 --> 00:26:30.970 basically only binds to the

NOTE Confidence: 0.96826357

00:26:30.970 --> 00:26:32.090 tetramer and not to the

NOTE Confidence: 0.96826357

00:26:32.090 --> 00:26:33.770 monomer forms, and then the

NOTE Confidence: 0.96826357

00:26:33.770 --> 00:26:35.390 turbidity is detected photometrically.

NOTE Confidence: 0.99007076

00:26:36.330 --> 00:26:38.010 And because this reflects the

NOTE Confidence: 0.99007076

00:26:38.010 --> 00:26:39.869 total pool of circulating tetrameric

NOTE Confidence: 0.99007076

00:26:40.090 --> 00:26:40.590 TTR,

NOTE Confidence: 0.9912632

00:26:40.890 --> 00:26:42.490 it's been proposed as an

NOTE Confidence: 0.9912632

00:26:42.490 --> 00:26:44.830 indirect marker of tetramer stability.

NOTE Confidence: 0.99927926

00:26:45.225 --> 00:26:46.984 So we're assuming that the

NOTE Confidence: 0.99927926

00:26:46.984 --> 00:26:47.484 concentration

NOTE Confidence: 0.99352145

00:26:48.025 --> 00:26:49.165 equals stability.

NOTE Confidence: 0.9890259

00:26:49.705 --> 00:26:51.465 And in both hereditary and

NOTE Confidence: 0.9890259

00:26:51.465 --> 00:26:53.405 wild type ATTR, the pathogenic

NOTE Confidence: 0.9890259

00:26:53.625 --> 00:26:54.765 misfolding process

NOTE Confidence: 0.97054064

00:26:55.145 --> 00:26:57.325 eventually leads to lower plasma

NOTE Confidence: 0.97054064

00:26:57.385 --> 00:26:58.509 TTR concentrations,

NOTE Confidence: 0.99500597

00:26:59.129 --> 00:27:00.169 and that is thought to

NOTE Confidence: 0.99500597

00:27:00.169 --> 00:27:02.649 reflect ongoing tetramer dissociation and

NOTE Confidence: 0.99500597

00:27:02.649 --> 00:27:03.149 catabolism.

NOTE Confidence: 0.9660348

00:27:03.609 --> 00:27:04.809 And in fact, some studies

NOTE Confidence: 0.9660348

00:27:04.809 --> 00:27:06.250 have shown that the lower

NOTE Confidence: 0.9660348

00:27:06.250 --> 00:27:08.490 the plasma TTR is, that

NOTE Confidence: 0.9660348

00:27:08.490 --> 00:27:10.169 was associated with about one

NOTE Confidence: 0.9660348

00:27:10.169 --> 00:27:11.210 point five to one point

NOTE Confidence: 0.9660348

00:27:11.210 --> 00:27:13.165 six fold increase in actual

NOTE Confidence: 0.9660348

00:27:13.165 --> 00:27:14.225 incident heart failure.

NOTE Confidence: 0.9830511

00:27:15.805 --> 00:27:17.325 But I do wanna caution

NOTE Confidence: 0.9830511

00:27:17.325 --> 00:27:19.244 folks that interpreting this assay

NOTE Confidence: 0.9830511

00:27:19.244 --> 00:27:20.865 is quite tricky because TTR

NOTE Confidence: 0.9830511

00:27:20.925 --> 00:27:22.525 itself is a negative acute

NOTE Confidence: 0.9830511

00:27:22.525 --> 00:27:24.125 phase reactant, and it does

NOTE Confidence: 0.9830511

00:27:24.125 --> 00:27:25.265 fall with inflammation,

NOTE Confidence: 0.999864

00:27:25.859 --> 00:27:26.359 malnutrition,

NOTE Confidence: 0.99724275

00:27:26.740 --> 00:27:28.760 liver disease, and renal wasting.

NOTE Confidence: 0.99724275

00:27:28.900 --> 00:27:30.260 So low levels are not

NOTE Confidence: 0.99724275

00:27:30.260 --> 00:27:32.100 always specific for amyloid and

NOTE Confidence: 0.99724275

00:27:32.100 --> 00:27:33.220 should be interpreted in the

NOTE Confidence: 0.99724275

00:27:33.220 --> 00:27:34.520 right clinical context.

NOTE Confidence: 0.97853094

00:27:35.780 --> 00:27:37.700 The second assay that was

NOTE Confidence: 0.97853094

00:27:37.700 --> 00:27:38.200 developed

NOTE Confidence: 0.99670166

00:27:39.355 --> 00:27:40.174 is transthyretin

NOTE Confidence: 0.83701813

00:27:40.794 --> 00:27:41.294 unfolding,

NOTE Confidence: 0.97654015

00:27:41.755 --> 00:27:42.794 and this is a new

NOTE Confidence: 0.97654015

00:27:42.794 --> 00:27:44.394 class of assay that actually

NOTE Confidence: 0.97654015

00:27:44.394 --> 00:27:46.654 detects non native or misfolded

NOTE Confidence: 0.97654015

00:27:46.794 --> 00:27:47.294 transthyretin

NOTE Confidence: 0.99142647

00:27:47.835 --> 00:27:50.015 rather than total circulating TTR.

NOTE Confidence: 0.98938

00:27:50.394 --> 00:27:52.335 So once the tetramer dissociate

NOTE Confidence: 0.98938

00:27:52.475 --> 00:27:53.294 into monomers,

NOTE Confidence: 0.99886006

00:27:53.770 --> 00:27:55.369 these monomers can unfold and

NOTE Confidence: 0.99886006

00:27:55.369 --> 00:27:57.070 nucleate into small aggregates.

NOTE Confidence: 0.9968894

00:27:57.690 --> 00:27:58.970 That's the early step in

NOTE Confidence: 0.9968894

00:27:58.970 --> 00:27:59.470 amyloidogenesis

NOTE Confidence: 0.9736735

00:28:00.090 --> 00:28:01.230 as we had talked about.

NOTE Confidence: 0.9736735

00:28:01.290 --> 00:28:02.030 So this

NOTE Confidence: 0.82616407

00:28:02.490 --> 00:28:02.990 NNTTR

NOTE Confidence: 0.9945928

00:28:04.090 --> 00:28:04.590 assay,

NOTE Confidence: 0.9586827

00:28:04.890 --> 00:28:06.605 it uses a sandwich ELISA

NOTE Confidence: 0.9586827

00:28:06.665 --> 00:28:08.665 configuration where capture and detection

NOTE Confidence: 0.9586827

00:28:08.665 --> 00:28:10.585 antibodies are specific to epitopes

NOTE Confidence: 0.9586827

00:28:10.585 --> 00:28:12.425 that are only exposed in

NOTE Confidence: 0.9586827

00:28:12.425 --> 00:28:14.045 non native TTR confirmation.

NOTE Confidence: 0.99831176

00:28:14.585 --> 00:28:15.785 And this makes it highly

NOTE Confidence: 0.99831176

00:28:15.785 --> 00:28:18.445 specific for detecting misfolded tetramer

NOTE Confidence: 0.99831176

00:28:18.505 --> 00:28:19.005 fragments

NOTE Confidence: 0.86903334

00:28:19.560 --> 00:28:22.060 that circulate before fibro deposition.

NOTE Confidence: 0.97670346

00:28:23.640 --> 00:28:24.940 And in blinded testing,

NOTE Confidence: 0.9925151

00:28:25.320 --> 00:28:26.920 the actual assay was able

NOTE Confidence: 0.9925151

00:28:26.920 --> 00:28:28.220 to separate symptomatic

NOTE Confidence: 0.7711505

00:28:28.680 --> 00:28:30.680 val thirty met familial amyloid

NOTE Confidence: 0.7711505

00:28:30.680 --> 00:28:31.640 polyneuropathy from healthy controls and

NOTE Confidence: 0.7711505

00:28:31.640 --> 00:28:32.355 was able to

NOTE Confidence: 0.92490643

00:28:35.875 --> 00:28:37.554 carriers. And I'll point out

NOTE Confidence: 0.92490643

00:28:37.554 --> 00:28:39.075 to this, but, basically, you

NOTE Confidence: 0.92490643

00:28:39.075 --> 00:28:40.294 can see here in red

NOTE Confidence: 0.92490643

00:28:40.355 --> 00:28:41.255 the presymptomatic

NOTE Confidence: 0.88324845

00:28:41.875 --> 00:28:42.375 carriers

NOTE Confidence: 0.8405402

00:28:42.835 --> 00:28:44.375 and in green, the symptomatic

NOTE Confidence: 0.8405402

00:28:44.674 --> 00:28:45.174 untreated

NOTE Confidence: 0.9375538

00:28:45.809 --> 00:28:47.490 versus in age matched control,

NOTE Confidence: 0.9375538

00:28:47.490 --> 00:28:49.169 it's nearly nil. And so

NOTE Confidence: 0.9375538

00:28:49.169 --> 00:28:50.690 that's, again, one step into

NOTE Confidence: 0.9375538

00:28:50.690 --> 00:28:52.549 detecting preclinical disease.

NOTE Confidence: 0.9880344

00:28:53.009 --> 00:28:54.370 The only issue with this

NOTE Confidence: 0.9880344

00:28:54.370 --> 00:28:55.250 is that it was not

NOTE Confidence: 0.9880344

00:28:55.250 --> 00:28:57.330 really able to detect the

NOTE Confidence: 0.9880344

00:28:57.330 --> 00:28:58.549 TTR cardiomyopathic

NOTE Confidence: 0.81921065

00:29:00.210 --> 00:29:00.710 variant,

NOTE Confidence: 0.97729397

00:29:01.405 --> 00:29:02.705 but rather the polyneuropathy.

NOTE Confidence: 0.98422766

00:29:03.325 --> 00:29:05.105 But from a conceptual status,

NOTE Confidence: 0.98422766

00:29:05.165 --> 00:29:05.965 I think this is the

NOTE Confidence: 0.98422766

00:29:05.965 --> 00:29:07.165 type of assays that we

NOTE Confidence: 0.98422766

00:29:07.165 --> 00:29:08.765 are looking for, and this

NOTE Confidence: 0.98422766

00:29:08.765 --> 00:29:10.545 is a mechanism linked biomarker.

NOTE Confidence: 0.9677748

00:29:13.260 --> 00:29:14.780 And then finally, a third

NOTE Confidence: 0.9677748

00:29:14.780 --> 00:29:15.900 assay that I'm gonna talk

NOTE Confidence: 0.9677748

00:29:15.900 --> 00:29:17.440 about is measuring transthyretin

NOTE Confidence: 0.90985477

00:29:18.060 --> 00:29:19.420 aggregates or the TAD one

NOTE Confidence: 0.90985477

00:29:19.420 --> 00:29:21.340 detector. And this was developed

NOTE Confidence: 0.90985477

00:29:21.340 --> 00:29:23.020 out of the Silesis lab

NOTE Confidence: 0.90985477

00:29:23.020 --> 00:29:24.080 at UT Southwestern.

NOTE Confidence: 0.9966777

00:29:25.340 --> 00:29:26.960 This is a structure based

NOTE Confidence: 0.3018527

00:29:27.645 --> 00:29:28.145 floral

NOTE Confidence: 0.9565143

00:29:29.085 --> 00:29:31.245 fluorescent probe that was designed

NOTE Confidence: 0.9565143

00:29:31.245 --> 00:29:32.945 to bind to pathogenic TTR

NOTE Confidence: 0.9565143

00:29:33.085 --> 00:29:35.745 aggregates, the large beta sheet

NOTE Confidence: 0.9565143

00:29:35.805 --> 00:29:37.505 rich species that form downstream

NOTE Confidence: 0.9565143

00:29:37.565 --> 00:29:38.705 of tetramer dissociation.

NOTE Confidence: 0.9936202

00:29:40.020 --> 00:29:41.540 And using segments of the

NOTE Confidence: 0.9936202

00:29:41.540 --> 00:29:42.040 TTR

NOTE Confidence: 0.98421

00:29:42.580 --> 00:29:43.960 known to drive aggregation,

NOTE Confidence: 0.7815488

00:29:44.500 --> 00:29:46.340 researchers engineered the STAT one

NOTE Confidence: 0.7815488

00:29:46.340 --> 00:29:46.840 probe

NOTE Confidence: 0.997234

00:29:47.460 --> 00:29:49.060 that would recognize the episodes

NOTE Confidence: 0.997234

00:29:49.060 --> 00:29:50.580 that are exposed only in

NOTE Confidence: 0.997234

00:29:50.580 --> 00:29:51.080 amyloidogenic

NOTE Confidence: 0.96654403

00:29:51.620 --> 00:29:52.820 conformations and not in the

NOTE Confidence: 0.96654403

00:29:52.820 --> 00:29:53.640 native tetramers.

NOTE Confidence: 0.99677217

00:29:53.940 --> 00:29:55.140 And then they went ahead

NOTE Confidence: 0.95016617

00:29:55.725 --> 00:29:56.924 and, again, this is kind

NOTE Confidence: 0.95016617

00:29:56.924 --> 00:29:58.705 of explaining the whole assay

NOTE Confidence: 0.95016617

00:29:58.924 --> 00:29:59.825 where in amyloidosis

NOTE Confidence: 0.96355855

00:30:00.205 --> 00:30:02.225 patients, it binds and then

NOTE Confidence: 0.96355855

00:30:02.285 --> 00:30:03.725 it has a fluorescence with

NOTE Confidence: 0.96355855

00:30:03.725 --> 00:30:04.684 it that is able to

NOTE Confidence: 0.96355855

00:30:04.684 --> 00:30:05.345 be detected.

NOTE Confidence: 0.95997363

00:30:05.645 --> 00:30:06.684 And then they went ahead

NOTE Confidence: 0.95997363

00:30:06.684 --> 00:30:08.610 and did validation studies from

NOTE Confidence: 0.95997363

00:30:08.610 --> 00:30:10.050 the Cleveland Clinic and from

NOTE Confidence: 0.95997363

00:30:10.050 --> 00:30:11.490 UT Southwestern and were able

NOTE Confidence: 0.95997363

00:30:11.490 --> 00:30:13.490 to show that detected aggregates

NOTE Confidence: 0.95997363

00:30:13.490 --> 00:30:14.850 in plasma from both wild

NOTE Confidence: 0.95997363

00:30:14.850 --> 00:30:17.010 type and hereditary ATTR patients,

NOTE Confidence: 0.95997363

00:30:17.010 --> 00:30:18.230 but not in controls

NOTE Confidence: 0.7413607

00:30:18.530 --> 00:30:19.990 in AL amyloid doses,

NOTE Confidence: 0.9838036

00:30:20.290 --> 00:30:22.315 were higher. And importantly, in

NOTE Confidence: 0.9838036

00:30:22.315 --> 00:30:23.674 a subset of patients with

NOTE Confidence: 0.9838036

00:30:23.674 --> 00:30:24.174 asymptomatic

NOTE Confidence: 0.9225302

00:30:24.715 --> 00:30:25.215 aggregates,

NOTE Confidence: 0.95165783

00:30:25.595 --> 00:30:26.794 which is the one here

NOTE Confidence: 0.95165783

00:30:26.794 --> 00:30:28.715 in pink, they also showed

NOTE Confidence: 0.95165783

00:30:28.715 --> 00:30:30.634 a higher signal, suggesting that

NOTE Confidence: 0.95165783

00:30:30.634 --> 00:30:33.054 these aggregates again form before

NOTE Confidence: 0.95165783

00:30:33.115 --> 00:30:34.014 organ involvement.

NOTE Confidence: 0.9961645

00:30:36.389 --> 00:30:37.830 So let's shift gears towards

NOTE Confidence: 0.9961645

00:30:37.830 --> 00:30:38.330 imaging.

NOTE Confidence: 0.9995263

00:30:38.870 --> 00:30:39.990 What have we done in

NOTE Confidence: 0.9995263

00:30:39.990 --> 00:30:40.970 that area?

NOTE Confidence: 0.97404444

00:30:41.669 --> 00:30:43.669 In imaging, several amyloid PET

NOTE Confidence: 0.97404444

00:30:43.669 --> 00:30:45.669 tracers, which were initially designed

NOTE Confidence: 0.97404444

00:30:45.669 --> 00:30:47.190 for beta amyloid imaging in

NOTE Confidence: 0.97404444

00:30:47.190 --> 00:30:48.789 Alzheimer's disease, have now been

NOTE Confidence: 0.97404444

00:30:48.789 --> 00:30:49.289 repurposed

NOTE Confidence: 0.98250866

00:30:49.669 --> 00:30:51.284 to image systemic and cardiac

NOTE Confidence: 0.98250866

00:30:51.284 --> 00:30:51.784 amyloidosis.

NOTE Confidence: 0.9265038

00:30:53.125 --> 00:30:54.825 And compounds such as

NOTE Confidence: 0.96878815

00:30:55.525 --> 00:30:56.184 the Pittsburgh

NOTE Confidence: 0.9581271

00:30:56.645 --> 00:30:57.945 b compound,

NOTE Confidence: 0.881896

00:30:59.125 --> 00:30:59.865 the florbidapine,

NOTE Confidence: 0.88354397

00:31:00.485 --> 00:31:01.065 the florbidapyr,

NOTE Confidence: 0.89161974

00:31:01.684 --> 00:31:02.424 and the

NOTE Confidence: 0.9268924

00:31:03.030 --> 00:31:03.530 flutemetamol

NOTE Confidence: 0.8585195

00:31:04.310 --> 00:31:05.530 are all thiamflavine,

NOTE Confidence: 0.96923965

00:31:06.790 --> 00:31:07.290 like,

NOTE Confidence: 0.984361

00:31:07.830 --> 00:31:08.330 molecules.

NOTE Confidence: 0.9587935

00:31:09.270 --> 00:31:10.950 And thiamflavine is a classic

NOTE Confidence: 0.9587935

00:31:10.950 --> 00:31:12.710 histologic dye which binds to

NOTE Confidence: 0.9587935

00:31:12.710 --> 00:31:13.850 beta sheet fibrils,

NOTE Confidence: 0.98276323

00:31:14.470 --> 00:31:16.410 and they have these fibril

NOTE Confidence: 0.98276323

00:31:16.630 --> 00:31:18.010 sheet binding characteristics.

NOTE Confidence: 0.9854654

00:31:18.955 --> 00:31:21.195 These tracers recognize common structural

NOTE Confidence: 0.9854654

00:31:21.195 --> 00:31:22.955 motif on amyloid fibrils, most

NOTE Confidence: 0.9854654

00:31:22.955 --> 00:31:24.575 likely the beta sheet channels,

NOTE Confidence: 0.9854654

00:31:24.795 --> 00:31:26.415 so their uptake is independent

NOTE Confidence: 0.9941104

00:31:26.715 --> 00:31:27.535 of the precursors.

NOTE Confidence: 0.94325227

00:31:28.235 --> 00:31:29.775 And, notably, flutemetamol

NOTE Confidence: 0.99911755

00:31:30.235 --> 00:31:31.995 can bind to multiple amyloid

NOTE Confidence: 0.99911755

00:31:31.995 --> 00:31:32.975 binding sites.

NOTE Confidence: 0.99354666

00:31:34.370 --> 00:31:35.649 On the left bottom hand

NOTE Confidence: 0.99354666

00:31:35.649 --> 00:31:36.470 side is

NOTE Confidence: 0.7249074

00:31:37.010 --> 00:31:37.510 evizematide,

NOTE Confidence: 0.9810517

00:31:38.130 --> 00:31:39.590 which is a novel tracer,

NOTE Confidence: 0.9810517

00:31:39.809 --> 00:31:40.929 also known as p five

NOTE Confidence: 0.9810517

00:31:40.929 --> 00:31:42.929 plus fourteen, and this was

NOTE Confidence: 0.9810517

00:31:42.929 --> 00:31:45.409 developed specifically for systemic amyloid.

NOTE Confidence: 0.9810517

00:31:45.409 --> 00:31:46.549 And unlike the thioflavin

NOTE Confidence: 0.92286676

00:31:46.850 --> 00:31:47.350 analogs,

NOTE Confidence: 0.99823314

00:31:47.855 --> 00:31:48.835 it targets glycosaminoglycans

NOTE Confidence: 0.861196

00:31:49.775 --> 00:31:51.635 which decorate amyloid fibrils,

NOTE Confidence: 0.9892332

00:31:52.015 --> 00:31:54.175 offering potentially a universal and

NOTE Confidence: 0.9892332

00:31:54.175 --> 00:31:55.855 more organ agnostic marker of

NOTE Confidence: 0.9892332

00:31:55.855 --> 00:31:56.835 amyloid burden.

NOTE Confidence: 0.9788909

00:31:58.095 --> 00:31:59.055 And I won't go into

NOTE Confidence: 0.9788909

00:31:59.055 --> 00:32:00.595 the details of the thioflavin

NOTE Confidence: 0.9608518

00:32:00.895 --> 00:32:02.940 analogs, analogs, but, essentially, they

NOTE Confidence: 0.9608518

00:32:02.940 --> 00:32:03.840 have been shown

NOTE Confidence: 0.9643278

00:32:04.140 --> 00:32:05.760 to bind both the ATTR

NOTE Confidence: 0.9643278

00:32:05.980 --> 00:32:06.880 and AL.

NOTE Confidence: 0.9984408

00:32:07.740 --> 00:32:08.240 And

NOTE Confidence: 0.6016

00:32:08.620 --> 00:32:09.120 florvedepyr

NOTE Confidence: 0.9158839

00:32:09.420 --> 00:32:10.620 has shown to also bind

NOTE Confidence: 0.9158839

00:32:10.620 --> 00:32:11.440 non specifically

NOTE Confidence: 0.9980857

00:32:12.060 --> 00:32:13.580 in wild type patients as

NOTE Confidence: 0.9980857

00:32:13.580 --> 00:32:14.080 well.

NOTE Confidence: 0.9471105

00:32:15.495 --> 00:32:17.415 The compound b Pittsburgh was

NOTE Confidence: 0.9471105

00:32:17.415 --> 00:32:18.795 also shown in trials

NOTE Confidence: 0.98677945

00:32:19.095 --> 00:32:19.835 right here,

NOTE Confidence: 0.98152083

00:32:20.215 --> 00:32:21.575 where it was tested in

NOTE Confidence: 0.98152083

00:32:21.575 --> 00:32:23.275 a very small patient population.

NOTE Confidence: 0.98152083

00:32:23.335 --> 00:32:25.035 So six patients with ATTR

NOTE Confidence: 0.9611946

00:32:25.575 --> 00:32:26.950 and five patients with AL

NOTE Confidence: 0.9611946

00:32:26.950 --> 00:32:28.490 amyloid, both in preclinical

NOTE Confidence: 0.9709598

00:32:28.790 --> 00:32:29.290 disease.

NOTE Confidence: 0.97684205

00:32:29.670 --> 00:32:30.790 And about one third of

NOTE Confidence: 0.97684205

00:32:30.790 --> 00:32:32.170 the patients visually

NOTE Confidence: 0.9580185

00:32:32.630 --> 00:32:34.010 were thought to have disease,

NOTE Confidence: 0.9920236

00:32:34.310 --> 00:32:35.830 one third were deemed by

NOTE Confidence: 0.9920236

00:32:35.830 --> 00:32:37.110 fifty percent of the reader

NOTE Confidence: 0.9920236

00:32:37.110 --> 00:32:38.230 to have disease, and one

NOTE Confidence: 0.9920236

00:32:38.230 --> 00:32:39.270 third were thought to not

NOTE Confidence: 0.9920236

00:32:39.270 --> 00:32:41.015 have disease. So, again, some

NOTE Confidence: 0.9920236

00:32:41.015 --> 00:32:43.835 potential about detecting preclinical disease.

NOTE Confidence: 0.9488069

00:32:44.775 --> 00:32:46.395 But how about evozematide?

NOTE Confidence: 0.9868214

00:32:47.015 --> 00:32:49.095 And this is basically one

NOTE Confidence: 0.9868214

00:32:49.095 --> 00:32:51.195 of the most exciting tracers,

NOTE Confidence: 0.9868214

00:32:51.335 --> 00:32:52.294 I would say, in the

NOTE Confidence: 0.9868214

00:32:52.294 --> 00:32:53.895 field. And as I said,

NOTE Confidence: 0.9868214

00:32:53.895 --> 00:32:55.835 it decorates the amyloid fibril.

NOTE Confidence: 0.9172245

00:32:57.149 --> 00:32:58.190 In a rest in a

NOTE Confidence: 0.9172245

00:32:58.190 --> 00:32:59.169 recent retrospective

NOTE Confidence: 0.99829334

00:32:59.630 --> 00:33:01.389 pilot study of twenty five

NOTE Confidence: 0.99829334

00:33:01.389 --> 00:33:01.889 patients,

NOTE Confidence: 0.98353666

00:33:02.190 --> 00:33:04.110 seven that are ATTR wild

NOTE Confidence: 0.98353666

00:33:04.110 --> 00:33:04.610 type,

NOTE Confidence: 0.9960749

00:33:06.029 --> 00:33:07.730 it was capable of imaging

NOTE Confidence: 0.9960749

00:33:07.789 --> 00:33:09.950 systemic and cardiac amyloid across

NOTE Confidence: 0.9960749

00:33:09.950 --> 00:33:11.090 precursor types.

NOTE Confidence: 0.8840549

00:33:11.815 --> 00:33:12.795 And remarkably,

NOTE Confidence: 0.99072826

00:33:13.175 --> 00:33:14.455 it was able to detect

NOTE Confidence: 0.99072826

00:33:14.455 --> 00:33:16.295 cardiac uptake in all seven

NOTE Confidence: 0.99072826

00:33:16.295 --> 00:33:18.395 patients that are phenotype negative

NOTE Confidence: 0.99072826

00:33:18.455 --> 00:33:18.955 carriers,

NOTE Confidence: 0.9458162

00:33:19.335 --> 00:33:20.795 indicating that evozematide

NOTE Confidence: 0.99945277

00:33:21.095 --> 00:33:23.415 may visualize amyloid deposits before

NOTE Confidence: 0.99945277

00:33:23.415 --> 00:33:23.915 conventional

NOTE Confidence: 0.99887824

00:33:24.455 --> 00:33:24.955 radionuclide

NOTE Confidence: 0.9994954

00:33:25.415 --> 00:33:25.915 imaging.

NOTE Confidence: 0.97983414

00:33:26.580 --> 00:33:28.100 So this really represents a

NOTE Confidence: 0.97983414

00:33:28.100 --> 00:33:29.000 major advance,

NOTE Confidence: 0.95137155

00:33:29.460 --> 00:33:31.940 moving beyond indirect surrogates like

NOTE Confidence: 0.95137155

00:33:31.940 --> 00:33:33.700 calcium or phosphate binding to

NOTE Confidence: 0.95137155

00:33:33.700 --> 00:33:35.640 direct molecular visualization

NOTE Confidence: 0.99928105

00:33:36.020 --> 00:33:37.799 of the amyloid matrix itself.

NOTE Confidence: 0.9661569

00:33:39.445 --> 00:33:41.045 And, in fact, there's now

NOTE Confidence: 0.9661569

00:33:41.045 --> 00:33:42.725 the study called REVEAL, which

NOTE Confidence: 0.9661569

00:33:42.725 --> 00:33:43.785 we are a part of,

NOTE Confidence: 0.97911394

00:33:44.325 --> 00:33:45.765 which stands for I twenty

NOTE Confidence: 0.97911394

00:33:45.925 --> 00:33:47.305 I one twenty four evizematide.

NOTE Confidence: 0.9885798

00:33:48.005 --> 00:33:49.365 It's being tested in a

NOTE Confidence: 0.9885798

00:33:49.365 --> 00:33:50.665 large trial,

NOTE Confidence: 0.99676484

00:33:51.350 --> 00:33:52.870 that plans to enroll about

NOTE Confidence: 0.99676484

00:33:52.870 --> 00:33:54.570 two hundred patients with suspected

NOTE Confidence: 0.99676484

00:33:54.710 --> 00:33:55.610 cardiac amyloidosis.

NOTE Confidence: 0.9947188

00:33:55.990 --> 00:33:57.370 So you can't go in

NOTE Confidence: 0.9947188

00:33:57.510 --> 00:33:58.730 if you have an established

NOTE Confidence: 0.9947188

00:33:58.950 --> 00:34:01.190 diagnosis of cardiac amyloid. You

NOTE Confidence: 0.9947188

00:34:01.190 --> 00:34:02.710 get a single dose of

NOTE Confidence: 0.9947188

00:34:02.710 --> 00:34:03.370 the tracer,

NOTE Confidence: 0.9969429

00:34:03.904 --> 00:34:05.264 and the primary outcome is

NOTE Confidence: 0.9969429

00:34:05.264 --> 00:34:06.865 basically the efficacy and the

NOTE Confidence: 0.9969429

00:34:06.865 --> 00:34:07.365 sensitivity

NOTE Confidence: 0.9918956

00:34:07.904 --> 00:34:09.344 for the diagnosis of cardiac

NOTE Confidence: 0.9918956

00:34:09.344 --> 00:34:09.844 amyloidosis,

NOTE Confidence: 0.97499704

00:34:10.145 --> 00:34:11.344 but it's also looking at

NOTE Confidence: 0.97499704

00:34:11.344 --> 00:34:13.505 secondary outcomes such as adverse

NOTE Confidence: 0.97499704

00:34:13.505 --> 00:34:14.484 effects predominantly,

NOTE Confidence: 0.9869264

00:34:15.344 --> 00:34:16.464 of the tracer as well

NOTE Confidence: 0.9869264

00:34:16.464 --> 00:34:18.244 as kidney and liver function.

NOTE Confidence: 0.99962425

00:34:18.870 --> 00:34:20.470 And the goal is to

NOTE Confidence: 0.99962425

00:34:20.470 --> 00:34:21.450 understand whether

NOTE Confidence: 0.9486401

00:34:22.710 --> 00:34:23.750 evozematide can serve as a

NOTE Confidence: 0.9486401

00:34:23.750 --> 00:34:24.890 first line, noninvasive

NOTE Confidence: 0.99344355

00:34:25.190 --> 00:34:27.110 diagnostic tool for systemic and

NOTE Confidence: 0.99344355

00:34:27.110 --> 00:34:28.090 cardiac amyloidosis,

NOTE Confidence: 0.9973261

00:34:28.710 --> 00:34:30.730 potentially transforming how we identify

NOTE Confidence: 0.9973261

00:34:30.870 --> 00:34:32.390 disease much earlier in the

NOTE Confidence: 0.9973261

00:34:32.390 --> 00:34:32.890 course.

NOTE Confidence: 0.9994824

00:34:34.094 --> 00:34:35.135 And let's move a little

NOTE Confidence: 0.9994824

00:34:35.135 --> 00:34:36.675 bit to artificial intelligence.

NOTE Confidence: 0.9749336

00:34:36.975 --> 00:34:38.815 So multiple studies have been

NOTE Confidence: 0.9749336

00:34:38.815 --> 00:34:40.494 done in this space, including

NOTE Confidence: 0.9749336

00:34:40.494 --> 00:34:41.235 our own,

NOTE Confidence: 0.9051771

00:34:41.614 --> 00:34:43.875 doctor Aikunumu and doctor Kira,

NOTE Confidence: 0.8995084

00:34:44.175 --> 00:34:44.994 from the cardiovascular

NOTE Confidence: 0.995922

00:34:45.295 --> 00:34:46.515 data science lab,

NOTE Confidence: 0.9566562

00:34:47.780 --> 00:34:48.739 which was published in the

NOTE Confidence: 0.9566562

00:34:48.739 --> 00:34:50.600 European Heart Journal this year.

NOTE Confidence: 0.9566562

00:34:50.900 --> 00:34:52.739 And this study asked essentially

NOTE Confidence: 0.9566562

00:34:52.739 --> 00:34:54.900 whether AI enabled EKG, so

NOTE Confidence: 0.9566562

00:34:54.900 --> 00:34:57.060 AI EKG over here, or

NOTE Confidence: 0.9566562

00:34:57.060 --> 00:34:59.175 AI enabled EKG could detect

NOTE Confidence: 0.9566562

00:34:59.255 --> 00:35:01.275 preclinical transpiriting cardiomyopathy

NOTE Confidence: 0.9985383

00:35:01.975 --> 00:35:04.235 before traditional diagnostic imaging.

NOTE Confidence: 0.9909457

00:35:05.015 --> 00:35:06.955 Using routinely acquired TTE

NOTE Confidence: 0.93682194

00:35:07.335 --> 00:35:09.094 and EKG images for patients

NOTE Confidence: 0.93682194

00:35:09.094 --> 00:35:10.635 which were later and eventually

NOTE Confidence: 0.93682194

00:35:10.775 --> 00:35:11.915 referred for nucleotide

NOTE Confidence: 0.82736397

00:35:12.375 --> 00:35:13.915 for nuclei nuclei,

NOTE Confidence: 0.8884131

00:35:14.719 --> 00:35:15.619 amyloid testing,

NOTE Confidence: 0.99161536

00:35:16.239 --> 00:35:17.839 deep learning models were trained

NOTE Confidence: 0.99161536

00:35:17.839 --> 00:35:19.920 to recognize subtle structural and

NOTE Confidence: 0.99161536

00:35:19.920 --> 00:35:22.339 electrical patterns of ATTR cardiomyopathy.

NOTE Confidence: 0.95162076

00:35:23.119 --> 00:35:24.400 And the key question whether

NOTE Confidence: 0.95162076

00:35:24.400 --> 00:35:26.099 these AI derived signatures

NOTE Confidence: 0.9390882

00:35:26.640 --> 00:35:28.819 diverged before overt disease.

NOTE Confidence: 0.98792

00:35:29.424 --> 00:35:31.424 Essentially, could we protect predict

NOTE Confidence: 0.98792

00:35:31.424 --> 00:35:33.025 ATTR cardiac amyloid two to

NOTE Confidence: 0.98792

00:35:33.025 --> 00:35:34.724 three years before it's clinically

NOTE Confidence: 0.98792

00:35:34.785 --> 00:35:35.285 recognized?

NOTE Confidence: 0.9966811

00:35:35.904 --> 00:35:37.344 And this is basically what

NOTE Confidence: 0.9966811

00:35:37.344 --> 00:35:38.864 they show. In over one

NOTE Confidence: 0.9966811

00:35:38.864 --> 00:35:40.625 thousand seven hundred patients from

NOTE Confidence: 0.9966811

00:35:40.625 --> 00:35:42.885 both Yale and Houston Methodist,

NOTE Confidence: 0.99271894

00:35:43.880 --> 00:35:45.480 They show here that the

NOTE Confidence: 0.99271894

00:35:45.480 --> 00:35:47.900 AI predicted probability of ATTR

NOTE Confidence: 0.99271894

00:35:47.960 --> 00:35:48.860 cardiac amyloidosis

NOTE Confidence: 0.998045

00:35:49.239 --> 00:35:50.920 is much higher in those

NOTE Confidence: 0.998045

00:35:50.920 --> 00:35:51.739 who eventually

NOTE Confidence: 0.9738372

00:35:52.120 --> 00:35:53.900 progressed to have cardiac amyloid,

NOTE Confidence: 0.9738372

00:35:54.120 --> 00:35:55.420 and this was even predicted

NOTE Confidence: 0.9738372

00:35:55.640 --> 00:35:57.239 up to five years prior

NOTE Confidence: 0.9738372

00:35:57.239 --> 00:35:59.180 to their actual amyloid diagnosis.

NOTE Confidence: 0.9737938

00:35:59.855 --> 00:36:01.295 They also show that a

NOTE Confidence: 0.9737938

00:36:01.295 --> 00:36:03.775 double negative screen, meaning AI

NOTE Confidence: 0.9737938

00:36:03.775 --> 00:36:05.375 is AI EKG is negative

NOTE Confidence: 0.9737938

00:36:05.375 --> 00:36:06.914 and AI echo is negative,

NOTE Confidence: 0.9737938

00:36:07.055 --> 00:36:08.515 achieved a ninety percent

NOTE Confidence: 0.9997224

00:36:08.815 --> 00:36:09.315 sensitivity

NOTE Confidence: 0.95087487

00:36:09.614 --> 00:36:11.950 effectively ruling out disease, whereas

NOTE Confidence: 0.95087487

00:36:11.950 --> 00:36:13.630 a double positive screen had

NOTE Confidence: 0.95087487

00:36:13.630 --> 00:36:14.590 a more than eighty five

NOTE Confidence: 0.95087487

00:36:14.590 --> 00:36:15.650 percent specificity

NOTE Confidence: 0.98718965

00:36:16.030 --> 00:36:17.890 identifying those at highest risk.

NOTE Confidence: 0.99602854

00:36:18.350 --> 00:36:20.350 These results demonstrate that AI

NOTE Confidence: 0.99602854

00:36:20.350 --> 00:36:22.290 derived EKG and echo phenotypes

NOTE Confidence: 0.99602854

00:36:22.350 --> 00:36:24.030 can act as dynamic and

NOTE Confidence: 0.99602854

00:36:24.030 --> 00:36:25.170 scalable biomarkers

NOTE Confidence: 0.988636

00:36:25.605 --> 00:36:27.285 for tracking disease progression and

NOTE Confidence: 0.988636

00:36:27.285 --> 00:36:29.225 potentially guiding early evaluation

NOTE Confidence: 0.9764679

00:36:29.844 --> 00:36:31.065 and preventive therapy.

NOTE Confidence: 0.9677105

00:36:32.085 --> 00:36:33.765 And I actually went and

NOTE Confidence: 0.9677105

00:36:33.765 --> 00:36:36.265 tested our patient's EKG using

NOTE Confidence: 0.9677105

00:36:36.484 --> 00:36:37.225 the labs,

NOTE Confidence: 0.94342136

00:36:37.765 --> 00:36:40.185 both app and web based,

NOTE Confidence: 0.91181016

00:36:40.660 --> 00:36:42.660 and her probability of ATTR

NOTE Confidence: 0.91181016

00:36:42.660 --> 00:36:44.420 cardiac amyloid was about fifty

NOTE Confidence: 0.91181016

00:36:44.420 --> 00:36:45.160 some percent.

NOTE Confidence: 0.9712841

00:36:45.620 --> 00:36:47.000 So that is a positive

NOTE Confidence: 0.9712841

00:36:47.060 --> 00:36:47.560 screen,

NOTE Confidence: 0.98188734

00:36:48.020 --> 00:36:49.620 estimating about three to five

NOTE Confidence: 0.98188734

00:36:49.620 --> 00:36:51.400 fold higher odds of ATTR

NOTE Confidence: 0.98188734

00:36:51.540 --> 00:36:52.520 cardiac amyloidosis

NOTE Confidence: 0.9980923

00:36:52.900 --> 00:36:55.239 compared with AI negative patients.

NOTE Confidence: 0.98566604

00:36:57.174 --> 00:36:58.214 So let's all come back.

NOTE Confidence: 0.98566604

00:36:58.214 --> 00:36:58.934 I know I've talked a

NOTE Confidence: 0.98566604

00:36:58.934 --> 00:36:59.434 lot.

NOTE Confidence: 0.9801246

00:36:59.895 --> 00:37:01.094 But what does this all

NOTE Confidence: 0.9801246

00:37:01.094 --> 00:37:02.714 mean for our patient?

NOTE Confidence: 0.97786325

00:37:03.174 --> 00:37:04.295 Our sixty eight year old

NOTE Confidence: 0.97786325

00:37:04.295 --> 00:37:05.494 who's just in the office

NOTE Confidence: 0.97786325

00:37:05.494 --> 00:37:07.015 freaking out about her positive

NOTE Confidence: 0.97786325

00:37:07.015 --> 00:37:07.515 genetic

NOTE Confidence: 0.9883823

00:37:08.135 --> 00:37:09.869 testing results. Are we not

NOTE Confidence: 0.9883823

00:37:09.869 --> 00:37:11.390 gonna offer her anything? Are

NOTE Confidence: 0.9883823

00:37:11.390 --> 00:37:13.250 we gonna just only serially

NOTE Confidence: 0.9883823

00:37:13.390 --> 00:37:15.569 evaluate her? Because so far,

NOTE Confidence: 0.9883823

00:37:15.710 --> 00:37:16.690 none of the

NOTE Confidence: 0.9994199

00:37:17.469 --> 00:37:18.829 methods that I actually talked

NOTE Confidence: 0.9994199

00:37:18.829 --> 00:37:20.529 about are clinically available.

NOTE Confidence: 0.86203945

00:37:21.744 --> 00:37:22.484 So eventually,

NOTE Confidence: 0.99701166

00:37:23.025 --> 00:37:24.705 this patient actually did have

NOTE Confidence: 0.99701166

00:37:24.705 --> 00:37:25.364 an option.

NOTE Confidence: 0.9595382

00:37:25.665 --> 00:37:26.785 She was enrolled in the

NOTE Confidence: 0.9595382

00:37:26.785 --> 00:37:28.005 ACT Early trial.

NOTE Confidence: 0.91966534

00:37:28.625 --> 00:37:29.744 And the ACT Early is

NOTE Confidence: 0.91966534

00:37:29.744 --> 00:37:30.965 a prospective multinational

NOTE Confidence: 0.9328977

00:37:31.344 --> 00:37:34.065 randomized double blinded placebo controlled

NOTE Confidence: 0.9328977

00:37:34.065 --> 00:37:35.740 study that will test the

NOTE Confidence: 0.9328977

00:37:35.740 --> 00:37:37.280 hypothesis that prophylactic

NOTE Confidence: 0.9374067

00:37:37.580 --> 00:37:39.100 treatment with the next generation

NOTE Confidence: 0.9374067

00:37:39.100 --> 00:37:40.720 TTR stabilizer, ekoramidis,

NOTE Confidence: 0.8472487

00:37:41.500 --> 00:37:42.400 in asymptomatic

NOTE Confidence: 0.9941104

00:37:42.780 --> 00:37:44.780 again, asymptomatic carriers of a

NOTE Confidence: 0.9941104

00:37:44.780 --> 00:37:46.480 pathogenic TTR variant

NOTE Confidence: 0.9982091

00:37:46.835 --> 00:37:48.755 can prevent or delay the

NOTE Confidence: 0.9982091

00:37:48.755 --> 00:37:50.934 development of ATTR cardiac amyloidosis.

NOTE Confidence: 0.9960773

00:37:52.035 --> 00:37:53.094 Eligible patients

NOTE Confidence: 0.99118114

00:37:53.555 --> 00:37:54.375 should carry,

NOTE Confidence: 0.9666396

00:37:55.154 --> 00:37:56.914 a pathogenic TTR variant, should

NOTE Confidence: 0.9666396

00:37:56.914 --> 00:37:58.194 be within eighteen to seventy

NOTE Confidence: 0.9666396

00:37:58.194 --> 00:37:59.520 five years of age, and

NOTE Confidence: 0.9666396

00:37:59.520 --> 00:38:01.219 within ten years of this

NOTE Confidence: 0.9666396

00:38:01.360 --> 00:38:02.960 concept of predicted age of

NOTE Confidence: 0.9666396

00:38:02.960 --> 00:38:04.260 diagnosis or PATO.

NOTE Confidence: 0.9888535

00:38:05.520 --> 00:38:07.300 They will approximately randomize

NOTE Confidence: 0.69339496

00:38:07.600 --> 00:38:09.300 six hundred patients, at karameter

NOTE Confidence: 0.69339496

00:38:09.440 --> 00:38:10.420 versus placebo,

NOTE Confidence: 0.92182827

00:38:10.800 --> 00:38:12.640 and will perform serial cardiac

NOTE Confidence: 0.92182827

00:38:12.640 --> 00:38:14.500 and neurologic assessments, including

NOTE Confidence: 0.9832925

00:38:15.174 --> 00:38:17.594 cardiac radionuclide amyloid imaging with

NOTE Confidence: 0.9832925

00:38:17.654 --> 00:38:18.154 SPECT.

NOTE Confidence: 0.9928484

00:38:18.775 --> 00:38:20.075 And the primary

NOTE Confidence: 0.9337739

00:38:20.375 --> 00:38:22.214 efficacy endpoint is signed to

NOTE Confidence: 0.9337739

00:38:22.214 --> 00:38:23.515 development of ATTR

NOTE Confidence: 0.9607455

00:38:23.815 --> 00:38:24.315 cardiac

NOTE Confidence: 0.99304295

00:38:24.775 --> 00:38:25.275 amyloidosis

NOTE Confidence: 0.7756082

00:38:26.375 --> 00:38:27.515 by basically

NOTE Confidence: 0.96432406

00:38:27.815 --> 00:38:30.540 cardiac radionuclide imaging. And additional

NOTE Confidence: 0.96432406

00:38:30.540 --> 00:38:32.720 endpoints also include safety, tolerability,

NOTE Confidence: 0.96432406

00:38:33.020 --> 00:38:34.700 and effect on cardiac imaging

NOTE Confidence: 0.96432406

00:38:34.700 --> 00:38:37.520 parameters, serum TTR, nerve conduction,

NOTE Confidence: 0.96432406

00:38:37.580 --> 00:38:38.239 and neurofilament

NOTE Confidence: 0.97222537

00:38:38.620 --> 00:38:39.360 light chain.

NOTE Confidence: 0.9990708

00:38:40.780 --> 00:38:42.320 And what else is available

NOTE Confidence: 0.9990708

00:38:42.540 --> 00:38:43.360 in the market?

NOTE Confidence: 0.99942595

00:38:44.325 --> 00:38:45.285 I don't know if folks

NOTE Confidence: 0.99942595

00:38:45.285 --> 00:38:46.425 have heard about

NOTE Confidence: 0.7575025

00:38:46.805 --> 00:38:47.305 Nexgrin

NOTE Confidence: 0.677454

00:38:48.165 --> 00:38:48.665 zuclamerin.

NOTE Confidence: 0.9689552

00:38:49.205 --> 00:38:51.125 I think, like, the just

NOTE Confidence: 0.9689552

00:38:51.125 --> 00:38:52.565 the names here are killing

NOTE Confidence: 0.9689552

00:38:52.565 --> 00:38:54.405 me. But it's basically a

NOTE Confidence: 0.9689552

00:38:54.405 --> 00:38:55.465 CRISPR Cas9

NOTE Confidence: 0.9103893

00:38:55.925 --> 00:38:56.825 gene editing,

NOTE Confidence: 0.7528832

00:38:57.525 --> 00:38:58.425 based treatments.

NOTE Confidence: 0.9982236

00:38:59.570 --> 00:39:00.770 And this is probably one

NOTE Confidence: 0.9982236

00:39:00.770 --> 00:39:02.230 of the most exciting developments

NOTE Confidence: 0.9982236

00:39:02.290 --> 00:39:03.730 in the field. It's in

NOTE Confidence: 0.9982236

00:39:03.730 --> 00:39:04.230 vivo

NOTE Confidence: 0.9780816

00:39:04.530 --> 00:39:06.710 gene editing for transthyretin amyloidosis.

NOTE Confidence: 0.9780816

00:39:06.930 --> 00:39:08.370 So this approach uses a

NOTE Confidence: 0.9780816

00:39:08.370 --> 00:39:10.130 CRISPR Cas nine system. So

NOTE Confidence: 0.9780816

00:39:10.130 --> 00:39:11.410 for folks that are not

NOTE Confidence: 0.9780816

00:39:11.410 --> 00:39:13.170 really familiar with CRISPR Cas

NOTE Confidence: 0.9780816

00:39:13.170 --> 00:39:14.765 nine, it is usually delivered

NOTE Confidence: 0.9780816

00:39:14.765 --> 00:39:15.905 by lipid nanoparticles.

NOTE Confidence: 0.9690692

00:39:16.445 --> 00:39:18.145 It carries a messenger RNA

NOTE Confidence: 0.96672064

00:39:18.445 --> 00:39:19.885 for Cas nine and a

NOTE Confidence: 0.96672064

00:39:19.885 --> 00:39:21.245 guide RNA that is specific

NOTE Confidence: 0.96672064

00:39:21.245 --> 00:39:22.045 to the t t r

NOTE Confidence: 0.96672064

00:39:22.045 --> 00:39:23.645 gene. And so once inside

NOTE Confidence: 0.96672064

00:39:23.645 --> 00:39:24.385 the hepatocytes,

NOTE Confidence: 0.9320715

00:39:24.765 --> 00:39:26.445 Cas nine would introduce usually

NOTE Confidence: 0.9320715

00:39:26.445 --> 00:39:27.905 a small frame shift mutation

NOTE Confidence: 0.9798532

00:39:28.260 --> 00:39:30.180 and that permanently knocks out

NOTE Confidence: 0.9798532

00:39:30.180 --> 00:39:31.400 the TTR production,

NOTE Confidence: 0.99896276

00:39:32.260 --> 00:39:32.760 effectively

NOTE Confidence: 0.89868915

00:39:33.219 --> 00:39:34.440 a one time therapy.

NOTE Confidence: 0.9985805

00:39:35.219 --> 00:39:36.120 So the first

NOTE Confidence: 0.9613657

00:39:36.660 --> 00:39:37.480 in human

NOTE Confidence: 0.96072614

00:39:37.860 --> 00:39:39.940 study was published in twenty

NOTE Confidence: 0.96072614

00:39:39.940 --> 00:39:41.300 twenty one in New England

NOTE Confidence: 0.96072614

00:39:41.300 --> 00:39:42.920 Journal of Medicine by Gilmore

NOTE Confidence: 0.96072614

00:39:43.060 --> 00:39:43.800 et al.

NOTE Confidence: 0.8912415

00:39:44.415 --> 00:39:45.614 And they looked at, I

NOTE Confidence: 0.8912415

00:39:45.614 --> 00:39:46.114 believe,

NOTE Confidence: 0.9920581

00:39:46.575 --> 00:39:48.675 six patients with hereditary ATTR

NOTE Confidence: 0.9741661

00:39:49.135 --> 00:39:49.635 polyneuropathy.

NOTE Confidence: 0.9957981

00:39:50.415 --> 00:39:51.875 And after a single infusion,

NOTE Confidence: 0.9830031

00:39:52.255 --> 00:39:54.335 circulating TTR levels fell by

NOTE Confidence: 0.9830031

00:39:54.335 --> 00:39:55.775 up to eighty seven percent

NOTE Confidence: 0.9830031

00:39:55.775 --> 00:39:57.614 within four weeks with no

NOTE Confidence: 0.9830031

00:39:57.614 --> 00:39:59.155 serious safety events.

NOTE Confidence: 0.99829334

00:39:59.890 --> 00:40:01.650 Marking the first proof that

NOTE Confidence: 0.99829334

00:40:01.650 --> 00:40:02.930 CRISPR could be used safely

NOTE Confidence: 0.99829334

00:40:02.930 --> 00:40:03.590 in vivo.

NOTE Confidence: 0.9798145

00:40:04.609 --> 00:40:05.430 More recently,

NOTE Confidence: 0.9790241

00:40:05.810 --> 00:40:07.170 published in twenty twenty four

NOTE Confidence: 0.9790241

00:40:07.170 --> 00:40:08.369 was a follow-up phase one

NOTE Confidence: 0.9790241

00:40:08.369 --> 00:40:10.230 study by Fontana et al,

NOTE Confidence: 0.9790241

00:40:10.290 --> 00:40:11.910 and it extended this approach

NOTE Confidence: 0.9932038

00:40:12.395 --> 00:40:14.175 to patients with ATTR cardiomyopathy,

NOTE Confidence: 0.9965061

00:40:14.714 --> 00:40:16.415 both wild type and variant.

NOTE Confidence: 0.9672292

00:40:16.795 --> 00:40:18.494 They enrolled thirty six participants,

NOTE Confidence: 0.9689717

00:40:18.795 --> 00:40:20.315 and the mean TTR levels,

NOTE Confidence: 0.9689717

00:40:20.315 --> 00:40:21.355 as shown here on the

NOTE Confidence: 0.9689717

00:40:21.355 --> 00:40:22.175 bottom line,

NOTE Confidence: 0.9933274

00:40:22.635 --> 00:40:23.994 fell by more than ninety

NOTE Confidence: 0.9933274

00:40:23.994 --> 00:40:25.835 percent and remained suppressed for

NOTE Confidence: 0.9933274

00:40:25.835 --> 00:40:26.734 over a year

NOTE Confidence: 0.95094043

00:40:27.350 --> 00:40:29.030 with stable cardio with stable

NOTE Confidence: 0.95094043

00:40:29.030 --> 00:40:31.450 cardiac biomarkers and NYH class.

NOTE Confidence: 0.9988915

00:40:31.830 --> 00:40:33.750 Adverse events were generally mild

NOTE Confidence: 0.9988915

00:40:33.750 --> 00:40:35.450 and mostly limited to transfusion

NOTE Confidence: 0.9857767

00:40:35.750 --> 00:40:37.190 reactions. And while the trial

NOTE Confidence: 0.9857767

00:40:37.190 --> 00:40:39.270 reported ninety four percent of

NOTE Confidence: 0.9857767

00:40:39.270 --> 00:40:40.710 at least one adverse effects,

NOTE Confidence: 0.9857767

00:40:40.710 --> 00:40:41.925 most of them were actually

NOTE Confidence: 0.9857767

00:40:41.925 --> 00:40:42.825 amyloid events

NOTE Confidence: 0.9493812

00:40:43.205 --> 00:40:44.965 and fourteen percent only were

NOTE Confidence: 0.9493812

00:40:44.965 --> 00:40:46.105 transfusion reactions.

NOTE Confidence: 0.9874407

00:40:46.805 --> 00:40:47.545 And now

NOTE Confidence: 0.96089566

00:40:48.885 --> 00:40:50.805 we are, recruiting the phase

NOTE Confidence: 0.96089566

00:40:50.805 --> 00:40:52.425 three trial or the MAGNITUDE,

NOTE Confidence: 0.9727311

00:40:52.805 --> 00:40:54.344 which will actually tell us

NOTE Confidence: 0.9727311

00:40:54.485 --> 00:40:56.245 whether this translates into improved

NOTE Confidence: 0.9727311

00:40:56.245 --> 00:40:57.145 clinical outcomes.

NOTE Confidence: 0.9562441

00:40:58.590 --> 00:41:00.450 But overall, it's a remarkable

NOTE Confidence: 0.9562441

00:41:00.510 --> 00:41:02.830 step towards curative therapy for

NOTE Confidence: 0.9562441

00:41:02.830 --> 00:41:03.330 amyloid.

NOTE Confidence: 0.99906427

00:41:06.270 --> 00:41:07.570 And I hope

NOTE Confidence: 0.9880566

00:41:08.190 --> 00:41:10.270 that now by now, I

NOTE Confidence: 0.9880566

00:41:10.270 --> 00:41:11.710 was able to illustrate to

NOTE Confidence: 0.9880566

00:41:11.710 --> 00:41:12.210 you

NOTE Confidence: 0.99665093

00:41:12.635 --> 00:41:13.915 that what we see in

NOTE Confidence: 0.99665093

00:41:13.915 --> 00:41:14.415 clinic,

NOTE Confidence: 0.9996407

00:41:14.875 --> 00:41:15.614 heart failure,

NOTE Confidence: 0.912757

00:41:16.795 --> 00:41:18.494 shortness of breath, lower extremity

NOTE Confidence: 0.912757

00:41:18.555 --> 00:41:19.915 edema is only the tip

NOTE Confidence: 0.912757

00:41:19.915 --> 00:41:21.035 of the iceberg. And in

NOTE Confidence: 0.912757

00:41:21.035 --> 00:41:22.795 fact, it's preceded by month,

NOTE Confidence: 0.912757

00:41:22.795 --> 00:41:24.094 if not, if not years

NOTE Confidence: 0.77311563

00:41:24.395 --> 00:41:25.135 of underlying

NOTE Confidence: 0.89891297

00:41:25.660 --> 00:41:27.820 buildup of amyloid eventually leading

NOTE Confidence: 0.89891297

00:41:27.820 --> 00:41:28.560 to decompensation.

NOTE Confidence: 0.99789166

00:41:29.500 --> 00:41:30.540 And this is why we

NOTE Confidence: 0.99789166

00:41:30.540 --> 00:41:32.880 should totally focus on comprehensive

NOTE Confidence: 0.99789166

00:41:33.100 --> 00:41:35.020 amyloid care and referral to

NOTE Confidence: 0.99789166

00:41:35.020 --> 00:41:36.560 amyloid expert centers

NOTE Confidence: 0.96501344

00:41:36.860 --> 00:41:38.565 with a shameless plug to

NOTE Confidence: 0.96501344

00:41:38.565 --> 00:41:40.665 our Yale cardiac amyloidosis program

NOTE Confidence: 0.96501344

00:41:40.885 --> 00:41:41.844 that is led by our

NOTE Confidence: 0.96501344

00:41:41.844 --> 00:41:43.925 fearless leaders, doctor Gallegos and

NOTE Confidence: 0.96501344

00:41:43.925 --> 00:41:44.744 doctor Miller,

NOTE Confidence: 0.99127513

00:41:45.045 --> 00:41:46.025 and that truly,

NOTE Confidence: 0.9539321

00:41:46.964 --> 00:41:49.125 combines expertise not only across

NOTE Confidence: 0.9539321

00:41:49.125 --> 00:41:50.905 different fields but also within

NOTE Confidence: 0.9539321

00:41:51.204 --> 00:41:53.219 the cardiology section itself. This

NOTE Confidence: 0.9539321

00:41:53.219 --> 00:41:54.180 is the QR code. You

NOTE Confidence: 0.9539321

00:41:54.180 --> 00:41:55.640 can go into the website.

NOTE Confidence: 0.98677635

00:41:57.380 --> 00:41:59.060 And, actually, the program now

NOTE Confidence: 0.98677635

00:41:59.060 --> 00:42:00.440 offers multiple trials

NOTE Confidence: 0.8481259

00:42:00.820 --> 00:42:02.040 and, also, in

NOTE Confidence: 0.9615492

00:42:02.340 --> 00:42:04.100 collaboration with the cardiovascular data

NOTE Confidence: 0.9615492

00:42:04.100 --> 00:42:06.465 science lab, multiple studies for

NOTE Confidence: 0.9615492

00:42:06.465 --> 00:42:07.285 early detection

NOTE Confidence: 0.9586721

00:42:07.745 --> 00:42:10.145 and early introduction possibly of

NOTE Confidence: 0.9586721

00:42:10.145 --> 00:42:11.445 treatment to these patients.

NOTE Confidence: 0.9970951

00:42:12.385 --> 00:42:13.364 And with that

NOTE Confidence: 0.9728688

00:42:13.665 --> 00:42:15.425 and to close, I wanna

NOTE Confidence: 0.9728688

00:42:15.425 --> 00:42:17.525 share a forward looking view

NOTE Confidence: 0.9728688

00:42:17.665 --> 00:42:18.785 of how we might care

NOTE Confidence: 0.9728688

00:42:18.785 --> 00:42:20.465 for the TTR variant carriers

NOTE Confidence: 0.9728688

00:42:20.465 --> 00:42:21.205 in the future,

NOTE Confidence: 0.95723724

00:42:21.690 --> 00:42:23.770 particularly those who are gene

NOTE Confidence: 0.95723724

00:42:23.770 --> 00:42:26.010 positive but phenotype, quote, unquote,

NOTE Confidence: 0.95723724

00:42:26.010 --> 00:42:26.510 negative.

NOTE Confidence: 0.9981146

00:42:26.810 --> 00:42:27.710 In the future,

NOTE Confidence: 0.9959946

00:42:28.329 --> 00:42:29.790 a patient with a TTR

NOTE Confidence: 0.9959946

00:42:29.849 --> 00:42:31.849 variant presenting to you, you

NOTE Confidence: 0.9959946

00:42:31.849 --> 00:42:33.450 can potentially use an AI

NOTE Confidence: 0.9959946

00:42:33.450 --> 00:42:35.290 based tool that is based

NOTE Confidence: 0.9959946

00:42:35.290 --> 00:42:35.950 on genetics,

NOTE Confidence: 0.99938256

00:42:36.355 --> 00:42:36.855 proteomics,

NOTE Confidence: 0.9700336

00:42:37.315 --> 00:42:39.555 clinical factors, and predict not

NOTE Confidence: 0.9700336

00:42:39.555 --> 00:42:41.015 the age of disease onset,

NOTE Confidence: 0.9700336

00:42:41.075 --> 00:42:42.614 but the age of disease

NOTE Confidence: 0.773772

00:42:42.915 --> 00:42:43.895 fibral formation.

NOTE Confidence: 0.98253506

00:42:44.355 --> 00:42:45.555 And then based off of

NOTE Confidence: 0.98253506

00:42:45.555 --> 00:42:46.055 that,

NOTE Confidence: 0.9957226

00:42:47.315 --> 00:42:49.015 then use highly sensitive

NOTE Confidence: 0.99947625

00:42:49.770 --> 00:42:51.230 imaging and biomarkers

NOTE Confidence: 0.9965513

00:42:51.690 --> 00:42:53.230 to track disease progression.

NOTE Confidence: 0.9506141

00:42:53.610 --> 00:42:54.270 And, eventually,

NOTE Confidence: 0.9994722

00:42:54.890 --> 00:42:55.790 once amyloidogenesis

NOTE Confidence: 0.99923134

00:42:56.570 --> 00:42:58.170 begins, then we can also

NOTE Confidence: 0.99923134

00:42:58.170 --> 00:42:59.790 use AI based tools

NOTE Confidence: 0.9845483

00:43:00.410 --> 00:43:02.270 to select the optimal combination

NOTE Confidence: 0.9845483

00:43:02.330 --> 00:43:02.989 of therapy,

NOTE Confidence: 0.9836792

00:43:03.295 --> 00:43:05.875 single therapy, combination therapy, stabilizers,

NOTE Confidence: 0.94916505

00:43:07.295 --> 00:43:08.675 silencers, or degraders

NOTE Confidence: 0.92389673

00:43:08.975 --> 00:43:10.575 tailored to the patient's specific

NOTE Confidence: 0.92389673

00:43:10.575 --> 00:43:11.075 mutation,

NOTE Confidence: 0.8399028

00:43:11.455 --> 00:43:13.167 organ involvement, and predicted response

NOTE Confidence: 0.8399028

00:43:13.167 --> 00:43:13.795 profile. And, ultimately, gene repair

NOTE Confidence: 0.8399028

00:43:14.015 --> 00:43:14.515 therapies,

NOTE Confidence: 0.834657

00:43:17.680 --> 00:43:18.420 such as CRISPR

NOTE Confidence: 0.8471856

00:43:18.720 --> 00:43:19.940 based CTR correction,

NOTE Confidence: 0.90638965

00:43:20.320 --> 00:43:21.840 could move us from lifelong

NOTE Confidence: 0.90638965

00:43:21.840 --> 00:43:23.540 management to true prevention

NOTE Confidence: 0.78225195

00:43:24.000 --> 00:43:24.820 where amyloidosis

NOTE Confidence: 0.9533544

00:43:25.280 --> 00:43:26.739 never develops at all.

NOTE Confidence: 0.9582847

00:43:27.440 --> 00:43:29.275 This vision moves us more

NOTE Confidence: 0.9582847

00:43:29.275 --> 00:43:31.455 from reactive diagnosis to proactive

NOTE Confidence: 0.9245553

00:43:31.915 --> 00:43:33.135 personalized prevention.

NOTE Confidence: 0.9693145

00:43:34.715 --> 00:43:36.235 And finally, I would like

NOTE Confidence: 0.9693145

00:43:36.235 --> 00:43:38.155 to thank multitude and multitude

NOTE Confidence: 0.9693145

00:43:38.155 --> 00:43:39.614 of people, many of who

NOTE Confidence: 0.98282045

00:43:39.995 --> 00:43:41.355 are not really shown here,

NOTE Confidence: 0.98282045

00:43:41.355 --> 00:43:42.895 but have really helped me

NOTE Confidence: 0.98282045

00:43:43.140 --> 00:43:44.520 become who I am today

NOTE Confidence: 0.98282045

00:43:44.739 --> 00:43:46.180 and believed in me when

NOTE Confidence: 0.98282045

00:43:46.180 --> 00:43:47.380 even I didn't believe in

NOTE Confidence: 0.98282045

00:43:47.380 --> 00:43:47.880 myself.

NOTE Confidence: 0.9738139

00:43:48.579 --> 00:43:50.420 And, doctor Miller can really

NOTE Confidence: 0.9738139

00:43:50.420 --> 00:43:52.260 attest, but my path to

NOTE Confidence: 0.9738139

00:43:52.260 --> 00:43:53.719 being here was never straightforward.

NOTE Confidence: 0.9729098

00:43:54.099 --> 00:43:55.140 And in fact, we think

NOTE Confidence: 0.9729098

00:43:55.140 --> 00:43:56.579 we're only ninety five percent

NOTE Confidence: 0.9729098

00:43:56.579 --> 00:43:57.779 of the way to figuring

NOTE Confidence: 0.9729098

00:43:57.779 --> 00:43:59.275 out what I'm gonna do.

NOTE Confidence: 0.9922366

00:44:00.455 --> 00:44:01.975 But kudos to those folks

NOTE Confidence: 0.9922366

00:44:01.975 --> 00:44:03.415 who really, you know, stuck

NOTE Confidence: 0.9922366

00:44:03.415 --> 00:44:04.455 with me and helped me

NOTE Confidence: 0.9922366

00:44:04.455 --> 00:44:05.735 figure it out. And special

NOTE Confidence: 0.9922366

00:44:05.735 --> 00:44:06.715 thanks to my

NOTE Confidence: 0.979452

00:44:07.175 --> 00:44:09.655 family, my husband, my son,

NOTE Confidence: 0.979452

00:44:09.655 --> 00:44:11.275 and especially my mom

NOTE Confidence: 0.99596345

00:44:12.130 --> 00:44:13.730 for accompanying me and being

NOTE Confidence: 0.99596345

00:44:13.730 --> 00:44:15.430 my anchor in this immigrant

NOTE Confidence: 0.9630743

00:44:15.810 --> 00:44:16.710 mother physician

NOTE Confidence: 0.96991754

00:44:17.010 --> 00:44:19.170 journey. So thank you. And,

NOTE Confidence: 0.96991754

00:44:19.330 --> 00:44:20.369 with that, I'm happy to

NOTE Confidence: 0.96991754

00:44:20.369 --> 00:44:21.270 take any question.

NOTE Confidence: 0.87849265

00:44:36.484 --> 00:44:37.765 I'll get started. I get

NOTE Confidence: 0.87849265

00:44:37.765 --> 00:44:38.505 first steps.

NOTE Confidence: 0.8970152

00:44:39.380 --> 00:44:40.280 Wonderful presentation.

NOTE Confidence: 0.9886192

00:44:40.580 --> 00:44:42.120 I'm, of course, incredibly,

NOTE Confidence: 0.9521123

00:44:43.219 --> 00:44:43.719 biased,

NOTE Confidence: 0.9893128

00:44:44.340 --> 00:44:45.700 with this topic, but this

NOTE Confidence: 0.9893128

00:44:45.700 --> 00:44:47.080 was music to my ears.

NOTE Confidence: 0.96082276

00:44:47.460 --> 00:44:49.300 After my recent tour for,

NOTE Confidence: 0.96082276

00:44:49.300 --> 00:44:51.219 you know, national international meetings

NOTE Confidence: 0.96082276

00:44:51.219 --> 00:44:52.820 for AMLO for the last

NOTE Confidence: 0.96082276

00:44:52.820 --> 00:44:54.285 few months, This is by

NOTE Confidence: 0.96082276

00:44:54.285 --> 00:44:56.125 far one of the most

NOTE Confidence: 0.96082276

00:44:56.125 --> 00:44:57.665 beautifully put, comprehensive,

NOTE Confidence: 0.9899753

00:44:58.204 --> 00:45:00.224 patient centered talks on

NOTE Confidence: 0.9995932

00:45:00.605 --> 00:45:01.344 early detection

NOTE Confidence: 0.91683763

00:45:01.724 --> 00:45:03.405 and of preclinical disease and

NOTE Confidence: 0.91683763

00:45:03.405 --> 00:45:04.704 hereditary TTR.

NOTE Confidence: 0.9139221

00:45:05.405 --> 00:45:06.685 And we are very excited

NOTE Confidence: 0.9139221

00:45:06.685 --> 00:45:08.070 that, hopefully, that five percent

NOTE Confidence: 0.9139221

00:45:08.150 --> 00:45:09.350 that we haven't figured out

NOTE Confidence: 0.9139221

00:45:09.350 --> 00:45:09.850 yet,

NOTE Confidence: 0.9752446

00:45:10.150 --> 00:45:11.430 you might want to put

NOTE Confidence: 0.9752446

00:45:11.430 --> 00:45:13.450 that vision in the TTR

NOTE Confidence: 0.9752446

00:45:13.590 --> 00:45:14.950 program and, you know, with

NOTE Confidence: 0.9752446

00:45:14.950 --> 00:45:16.710 all your basic science, work.

NOTE Confidence: 0.9752446

00:45:16.710 --> 00:45:18.469 This is really incredible, and

NOTE Confidence: 0.9752446

00:45:18.469 --> 00:45:19.910 I, I think this is

NOTE Confidence: 0.9752446

00:45:19.910 --> 00:45:21.464 great. So I don't know

NOTE Confidence: 0.9752446

00:45:21.464 --> 00:45:22.535 if doctor Miller Thank you.

NOTE Confidence: 0.9752446

00:45:22.664 --> 00:45:23.164 Has

NOTE Confidence: 0.5378392

00:45:25.094 --> 00:45:25.594 the

NOTE Confidence: 0.991394

00:45:25.904 --> 00:45:26.404 incredible

NOTE Confidence: 0.9776827

00:45:28.334 --> 00:45:28.834 comments.

NOTE Confidence: 0.89898854

00:45:29.144 --> 00:45:30.184 Sorry, Omar. I saw you.

NOTE Confidence: 0.89898854

00:45:30.184 --> 00:45:30.904 You raised your hand, but

NOTE Confidence: 0.89898854

00:45:30.904 --> 00:45:31.704 I thought we can defer

NOTE Confidence: 0.89898854

00:45:31.704 --> 00:45:32.204 you.

NOTE Confidence: 0.96200067

00:45:37.300 --> 00:45:39.300 Amazing talk, Sarah. This was

NOTE Confidence: 0.96200067

00:45:39.300 --> 00:45:41.140 really, really educational. Very, very

NOTE Confidence: 0.96200067

00:45:41.140 --> 00:45:41.640 helpful.

NOTE Confidence: 0.9674405

00:45:42.260 --> 00:45:43.300 I have two questions. So

NOTE Confidence: 0.9674405

00:45:43.300 --> 00:45:44.100 the first one is when

NOTE Confidence: 0.9674405

00:45:44.100 --> 00:45:45.560 you're showing the the penetrance

NOTE Confidence: 0.9674405

00:45:45.859 --> 00:45:47.380 of the val one twenty

NOTE Confidence: 0.9674405

00:45:47.380 --> 00:45:47.859 two,

NOTE Confidence: 0.9701863

00:45:48.455 --> 00:45:49.575 mutation, it was like a

NOTE Confidence: 0.9701863

00:45:49.575 --> 00:45:50.855 range of seven to one

NOTE Confidence: 0.9701863

00:45:50.855 --> 00:45:51.594 hundred percent.

NOTE Confidence: 0.99188405

00:45:52.375 --> 00:45:53.815 How do we explain that

NOTE Confidence: 0.99188405

00:45:53.815 --> 00:45:55.415 very broad range, and how

NOTE Confidence: 0.99188405

00:45:55.415 --> 00:45:57.255 does, like, our pretest knowledge

NOTE Confidence: 0.99188405

00:45:57.255 --> 00:45:58.455 of the penetrance of each

NOTE Confidence: 0.99188405

00:45:58.455 --> 00:46:00.475 variant kind of inform

NOTE Confidence: 0.9938663

00:46:01.070 --> 00:46:02.350 how aggressive we'll be with

NOTE Confidence: 0.9938663

00:46:02.350 --> 00:46:03.250 this, like, preclinical

NOTE Confidence: 0.95804596

00:46:04.110 --> 00:46:05.390 Yeah. No, sir. This is

NOTE Confidence: 0.95804596

00:46:05.390 --> 00:46:06.590 a great question. I think

NOTE Confidence: 0.95804596

00:46:06.590 --> 00:46:08.190 this is mostly based on

NOTE Confidence: 0.95804596

00:46:08.190 --> 00:46:09.790 population study and I think

NOTE Confidence: 0.95804596

00:46:09.790 --> 00:46:11.570 was spread over, like, multiple

NOTE Confidence: 0.95804596

00:46:11.630 --> 00:46:13.250 years. And so our diagnosis

NOTE Confidence: 0.950949

00:46:13.790 --> 00:46:15.310 tools have really changed over

NOTE Confidence: 0.950949

00:46:15.310 --> 00:46:16.530 that time, and probably,

NOTE Confidence: 0.97786057

00:46:16.910 --> 00:46:18.085 you know, the penetrance of

NOTE Confidence: 0.97786057

00:46:18.085 --> 00:46:19.285 seven percent is not really

NOTE Confidence: 0.97786057

00:46:19.285 --> 00:46:20.905 accurate. But but who knows?

NOTE Confidence: 0.97786057

00:46:21.045 --> 00:46:22.185 But I think it also,

NOTE Confidence: 0.97786057

00:46:22.245 --> 00:46:24.325 as I kinda alluded to,

NOTE Confidence: 0.97786057

00:46:24.325 --> 00:46:25.685 depends a lot on this

NOTE Confidence: 0.97786057

00:46:25.685 --> 00:46:27.125 concept of, like, predicted age

NOTE Confidence: 0.97786057

00:46:27.125 --> 00:46:28.645 of disease onset and, like,

NOTE Confidence: 0.97786057

00:46:28.645 --> 00:46:30.025 what is the specific variant,

NOTE Confidence: 0.9659263

00:46:31.520 --> 00:46:32.560 and also, like, age of

NOTE Confidence: 0.9659263

00:46:32.560 --> 00:46:34.560 onset across the populations and

NOTE Confidence: 0.9659263

00:46:34.560 --> 00:46:35.920 across the patient's family, a

NOTE Confidence: 0.9659263

00:46:35.920 --> 00:46:36.739 lot of epigenetic

NOTE Confidence: 0.9960263

00:46:37.040 --> 00:46:38.739 factors, a lot of environmental

NOTE Confidence: 0.9960263

00:46:38.960 --> 00:46:39.460 factors.

NOTE Confidence: 0.98957413

00:46:40.239 --> 00:46:41.200 But the bottom line is

NOTE Confidence: 0.98957413

00:46:41.200 --> 00:46:42.319 I don't think there's anything

NOTE Confidence: 0.98957413

00:46:42.319 --> 00:46:43.520 that can tell you exactly

NOTE Confidence: 0.98957413

00:46:43.520 --> 00:46:44.900 when you're gonna have it,

NOTE Confidence: 0.9723961

00:46:45.594 --> 00:46:46.875 or if you're actually gonna

NOTE Confidence: 0.9723961

00:46:46.875 --> 00:46:47.915 have it, but it's a

NOTE Confidence: 0.9723961

00:46:47.915 --> 00:46:49.275 sort of combination of things.

NOTE Confidence: 0.9723961

00:46:49.275 --> 00:46:50.075 And that's kind of one

NOTE Confidence: 0.9723961

00:46:50.075 --> 00:46:51.435 of the areas where, hopefully,

NOTE Confidence: 0.9723961

00:46:51.435 --> 00:46:52.875 artificial intelligence may also be

NOTE Confidence: 0.9723961

00:46:52.875 --> 00:46:53.375 helpful.

NOTE Confidence: 0.987866

00:46:54.315 --> 00:46:55.594 One more question. So, it

NOTE Confidence: 0.987866

00:46:55.594 --> 00:46:56.955 was striking that the double

NOTE Confidence: 0.987866

00:46:56.955 --> 00:46:59.375 ELISA assay predicted the neuro

NOTE Confidence: 0.9583298

00:46:59.989 --> 00:47:01.349 amyloid Mhmm. But you said

NOTE Confidence: 0.9583298

00:47:01.349 --> 00:47:02.869 not the cardiac amyloid? Yeah.

NOTE Confidence: 0.9583298

00:47:02.869 --> 00:47:04.309 I think so. This was,

NOTE Confidence: 0.9583298

00:47:04.309 --> 00:47:05.190 I think, out of the

NOTE Confidence: 0.9583298

00:47:05.190 --> 00:47:06.630 Jeffreys lab, if if I'm

NOTE Confidence: 0.9583298

00:47:06.630 --> 00:47:08.730 not mistaken. Mhmm. But, basically,

NOTE Confidence: 0.9583298

00:47:08.790 --> 00:47:09.450 I think,

NOTE Confidence: 0.96541864

00:47:10.309 --> 00:47:11.750 for some reason, that is

NOTE Confidence: 0.96541864

00:47:11.750 --> 00:47:13.055 related to the type of

NOTE Confidence: 0.96541864

00:47:13.055 --> 00:47:14.815 fibril that is usually, like,

NOTE Confidence: 0.96541864

00:47:14.815 --> 00:47:16.015 different types of, like, type

NOTE Confidence: 0.96541864

00:47:16.015 --> 00:47:17.055 a and type b and

NOTE Confidence: 0.96541864

00:47:17.215 --> 00:47:18.655 Sure. Some of them being

NOTE Confidence: 0.96541864

00:47:18.655 --> 00:47:20.175 more, like, neuropathic and some

NOTE Confidence: 0.96541864

00:47:20.175 --> 00:47:21.155 other being cardiomyopathic.

NOTE Confidence: 0.98669654

00:47:21.695 --> 00:47:22.415 And I think that is

NOTE Confidence: 0.98669654

00:47:22.415 --> 00:47:23.695 probably related to why the

NOTE Confidence: 0.98669654

00:47:23.695 --> 00:47:24.575 assay picked up on the

NOTE Confidence: 0.98669654

00:47:24.575 --> 00:47:25.075 neuropathic,

NOTE Confidence: 0.9700982

00:47:25.535 --> 00:47:26.435 subtype option.

NOTE Confidence: 0.9235897

00:47:28.900 --> 00:47:30.340 I'll add my kudos. Really

NOTE Confidence: 0.9235897

00:47:30.340 --> 00:47:31.960 phenomenal talk, and I agree,

NOTE Confidence: 0.9235897

00:47:32.020 --> 00:47:32.520 Cessia.

NOTE Confidence: 0.99271274

00:47:32.980 --> 00:47:34.200 Having been to many,

NOTE Confidence: 0.8813715

00:47:35.140 --> 00:47:36.420 amyloid talks from the early

NOTE Confidence: 0.8813715

00:47:36.420 --> 00:47:37.460 days of went to famines,

NOTE Confidence: 0.8813715

00:47:37.460 --> 00:47:38.580 it was even being developed.

NOTE Confidence: 0.8813715

00:47:38.739 --> 00:47:40.500 This was exceptionally well done,

NOTE Confidence: 0.8813715

00:47:40.500 --> 00:47:41.320 so congratulations.

NOTE Confidence: 0.9083627

00:47:42.885 --> 00:47:44.185 Couple kind of

NOTE Confidence: 0.88505703

00:47:44.485 --> 00:47:46.585 practical questions. So you mentioned

NOTE Confidence: 0.88505703

00:47:46.725 --> 00:47:48.485 and you started discussions around

NOTE Confidence: 0.88505703

00:47:48.485 --> 00:47:50.185 cascade genetic screening.

NOTE Confidence: 0.9980771

00:47:50.725 --> 00:47:52.105 But can you tell us

NOTE Confidence: 0.9980771

00:47:52.165 --> 00:47:53.445 what your ideas are and

NOTE Confidence: 0.9980771

00:47:53.445 --> 00:47:55.145 what we're doing here regarding

NOTE Confidence: 0.9980771

00:47:55.205 --> 00:47:55.705 cascade

NOTE Confidence: 0.9916028

00:47:56.319 --> 00:47:58.239 phenotypic screening, I guess, when

NOTE Confidence: 0.9916028

00:47:58.239 --> 00:47:58.980 you identify

NOTE Confidence: 0.9918492

00:47:59.280 --> 00:48:00.020 this patient

NOTE Confidence: 0.98615104

00:48:00.640 --> 00:48:01.859 has lumbar stenosis

NOTE Confidence: 0.9777136

00:48:02.239 --> 00:48:02.719 and and,

NOTE Confidence: 0.98881036

00:48:03.280 --> 00:48:05.359 and bilateral carpal tunnel syndrome.

NOTE Confidence: 0.98881036

00:48:05.359 --> 00:48:05.859 So,

NOTE Confidence: 0.9991616

00:48:06.799 --> 00:48:07.940 what is our practice

NOTE Confidence: 0.99734

00:48:08.655 --> 00:48:10.335 at Yale currently in terms

NOTE Confidence: 0.99734

00:48:10.335 --> 00:48:11.695 of making sure those patients

NOTE Confidence: 0.99734

00:48:11.695 --> 00:48:12.195 are

NOTE Confidence: 0.99936134

00:48:12.495 --> 00:48:13.535 not just lost in the

NOTE Confidence: 0.99936134

00:48:13.535 --> 00:48:14.035 wilderness

NOTE Confidence: 0.97469527

00:48:14.335 --> 00:48:16.094 and, eventually show up to

NOTE Confidence: 0.97469527

00:48:16.094 --> 00:48:18.815 cardiology, but maybe phenotypically initially

NOTE Confidence: 0.97469527

00:48:18.815 --> 00:48:19.315 screened

NOTE Confidence: 0.99153584

00:48:20.094 --> 00:48:21.475 after that initial diagnosis?

NOTE Confidence: 0.9698007

00:48:21.800 --> 00:48:22.680 Yeah. No. I think that's

NOTE Confidence: 0.9698007

00:48:22.680 --> 00:48:23.640 an excellent question. So I

NOTE Confidence: 0.9698007

00:48:23.640 --> 00:48:24.760 think I'm gonna answer based

NOTE Confidence: 0.9698007

00:48:24.760 --> 00:48:26.119 on my personal experience. Like,

NOTE Confidence: 0.9698007

00:48:26.119 --> 00:48:27.239 I think doctor Miller and

NOTE Confidence: 0.9698007

00:48:27.239 --> 00:48:28.920 doctor g often joke about,

NOTE Confidence: 0.9698007

00:48:28.920 --> 00:48:30.040 like, every time they're on

NOTE Confidence: 0.9698007

00:48:30.040 --> 00:48:31.480 surveys, like, at least, like,

NOTE Confidence: 0.9698007

00:48:31.480 --> 00:48:32.920 all the amyloid patients pop

NOTE Confidence: 0.9698007

00:48:32.920 --> 00:48:33.420 up.

NOTE Confidence: 0.99072385

00:48:34.040 --> 00:48:35.325 So I think, like, first

NOTE Confidence: 0.99072385

00:48:35.325 --> 00:48:36.705 of all, just being aware

NOTE Confidence: 0.99072385

00:48:36.765 --> 00:48:37.585 of the disease,

NOTE Confidence: 0.97299415

00:48:37.964 --> 00:48:39.724 being aggressive about screening, and

NOTE Confidence: 0.97299415

00:48:39.724 --> 00:48:40.705 also being aggressive

NOTE Confidence: 0.9130262

00:48:41.165 --> 00:48:42.945 not only about, like, stopping

NOTE Confidence: 0.99726313

00:48:43.325 --> 00:48:44.464 when the radionuclide

NOTE Confidence: 0.97603273

00:48:44.765 --> 00:48:46.525 imaging is negative, but also

NOTE Confidence: 0.97603273

00:48:46.525 --> 00:48:48.445 pushing more towards biopsies and

NOTE Confidence: 0.97603273

00:48:48.445 --> 00:48:49.645 actually making sure that the

NOTE Confidence: 0.97603273

00:48:49.645 --> 00:48:51.380 patient is not a patient

NOTE Confidence: 0.97603273

00:48:51.380 --> 00:48:52.980 with cardiac amyloid. That's one.

NOTE Confidence: 0.97603273

00:48:52.980 --> 00:48:54.340 And I think number two,

NOTE Confidence: 0.97603273

00:48:54.340 --> 00:48:55.780 with the cardiovascular data science

NOTE Confidence: 0.97603273

00:48:55.780 --> 00:48:57.219 lab, my impression is that

NOTE Confidence: 0.97603273

00:48:57.219 --> 00:48:58.820 they're trying to scale this

NOTE Confidence: 0.97603273

00:48:58.820 --> 00:48:59.880 AI EKG,

NOTE Confidence: 0.9739868

00:49:01.380 --> 00:49:02.900 tool to actually use it

NOTE Confidence: 0.9739868

00:49:02.900 --> 00:49:04.420 routinely in clinic where you

NOTE Confidence: 0.9739868

00:49:04.420 --> 00:49:06.280 are actually able to predict,

NOTE Confidence: 0.93891245

00:49:08.465 --> 00:49:10.065 the probability of actually having

NOTE Confidence: 0.93891245

00:49:10.065 --> 00:49:11.265 cardiac amyloid. And I think

NOTE Confidence: 0.93891245

00:49:11.265 --> 00:49:12.385 that would be something very

NOTE Confidence: 0.93891245

00:49:12.385 --> 00:49:13.585 cool if it's can be

NOTE Confidence: 0.93891245

00:49:13.585 --> 00:49:14.545 brought to the clinic and

NOTE Confidence: 0.93891245

00:49:14.545 --> 00:49:16.565 integrated within our routine use.

NOTE Confidence: 0.93891245

00:49:16.705 --> 00:49:17.745 Yeah. But, you know, just

NOTE Confidence: 0.93891245

00:49:17.745 --> 00:49:18.945 to be double that for

NOTE Confidence: 0.93891245

00:49:19.105 --> 00:49:20.305 great response, but to be

NOTE Confidence: 0.93891245

00:49:20.305 --> 00:49:21.205 double that advocate,

NOTE Confidence: 0.93481547

00:49:22.020 --> 00:49:22.520 nobody,

NOTE Confidence: 0.99250937

00:49:23.700 --> 00:49:24.180 payers

NOTE Confidence: 0.9764452

00:49:24.500 --> 00:49:25.480 government or nongovernmental

NOTE Confidence: 0.9905214

00:49:25.780 --> 00:49:27.160 payers are gonna pay

NOTE Confidence: 0.99893445

00:49:27.660 --> 00:49:28.160 for

NOTE Confidence: 0.9347569

00:49:28.660 --> 00:49:30.280 tafamidis in a population

NOTE Confidence: 0.9995736

00:49:30.660 --> 00:49:32.280 that has this screen

NOTE Confidence: 0.98551524

00:49:33.300 --> 00:49:34.040 with no

NOTE Confidence: 0.9903281

00:49:34.485 --> 00:49:36.565 outcomes data. So it is

NOTE Confidence: 0.9903281

00:49:36.565 --> 00:49:37.065 fantastic

NOTE Confidence: 0.9496887

00:49:37.445 --> 00:49:38.885 to see the panoply of

NOTE Confidence: 0.9496887

00:49:38.885 --> 00:49:40.565 clinical trials and and great

NOTE Confidence: 0.9496887

00:49:40.645 --> 00:49:41.865 and I hope you're engaging

NOTE Confidence: 0.88483065

00:49:42.405 --> 00:49:43.445 in learning how to do

NOTE Confidence: 0.88483065

00:49:43.445 --> 00:49:44.805 those kind of trials day

NOTE Confidence: 0.88483065

00:49:44.805 --> 00:49:46.245 to day, like working with

NOTE Confidence: 0.88483065

00:49:46.245 --> 00:49:47.205 the beaker, so to speak,

NOTE Confidence: 0.88483065

00:49:47.285 --> 00:49:48.745 two on clinical trials management.

NOTE Confidence: 0.9257541

00:49:49.125 --> 00:49:49.365 But,

NOTE Confidence: 0.940758

00:49:50.000 --> 00:49:51.359 and enrolling those patients early

NOTE Confidence: 0.940758

00:49:51.359 --> 00:49:52.640 on is critical. But I'm

NOTE Confidence: 0.940758

00:49:52.640 --> 00:49:53.619 I'm curious around

NOTE Confidence: 0.96692836

00:49:54.480 --> 00:49:55.859 what we do with regards

NOTE Confidence: 0.96692836

00:49:55.920 --> 00:49:56.819 to symptom.

NOTE Confidence: 0.99388564

00:49:57.119 --> 00:49:57.619 Yes.

NOTE Confidence: 0.89900225

00:49:58.640 --> 00:49:59.599 Do you you said they

NOTE Confidence: 0.89900225

00:49:59.599 --> 00:50:00.339 were asymptomatic,

NOTE Confidence: 0.99649256

00:50:00.640 --> 00:50:02.180 but how do you define

NOTE Confidence: 0.9933815

00:50:02.885 --> 00:50:03.704 someone asymptomatic

NOTE Confidence: 0.8652894

00:50:04.244 --> 00:50:05.045 in this? And and do

NOTE Confidence: 0.8652894

00:50:05.045 --> 00:50:06.405 you take them through exercise

NOTE Confidence: 0.8652894

00:50:06.405 --> 00:50:08.325 physiology or CPETs or anything

NOTE Confidence: 0.8652894

00:50:08.325 --> 00:50:09.605 like that? Yeah. I think,

NOTE Confidence: 0.8652894

00:50:09.605 --> 00:50:10.724 you know, I'll let doctor

NOTE Confidence: 0.8652894

00:50:10.724 --> 00:50:11.204 g,

NOTE Confidence: 0.94979376

00:50:11.605 --> 00:50:12.565 talk more, but I think

NOTE Confidence: 0.94979376

00:50:12.565 --> 00:50:14.005 that's kind of why this

NOTE Confidence: 0.94979376

00:50:14.005 --> 00:50:15.830 talk was really kind of

NOTE Confidence: 0.94979376

00:50:15.830 --> 00:50:18.310 anchored towards really developing better

NOTE Confidence: 0.94979376

00:50:18.310 --> 00:50:20.150 test novel technology that can

NOTE Confidence: 0.94979376

00:50:20.150 --> 00:50:21.370 define that asymptomatic,

NOTE Confidence: 0.89434135

00:50:22.469 --> 00:50:24.070 stage essentially, where it's really

NOTE Confidence: 0.973854

00:50:24.710 --> 00:50:26.070 what we define as symptomatic

NOTE Confidence: 0.973854

00:50:26.070 --> 00:50:27.510 is really just late onset

NOTE Confidence: 0.973854

00:50:27.510 --> 00:50:28.630 cardiac amyloid and kind of

NOTE Confidence: 0.973854

00:50:28.630 --> 00:50:29.750 pushing the needle a little

NOTE Confidence: 0.973854

00:50:29.750 --> 00:50:30.410 bit further.

NOTE Confidence: 0.9789642

00:50:30.975 --> 00:50:32.415 Yeah. So to answer the

NOTE Confidence: 0.9789642

00:50:32.575 --> 00:50:34.095 there's, like, two additional things

NOTE Confidence: 0.9789642

00:50:34.095 --> 00:50:35.295 that we're doing. In my

NOTE Confidence: 0.9789642

00:50:35.295 --> 00:50:36.355 fellow time,

NOTE Confidence: 0.9563588

00:50:36.735 --> 00:50:38.275 doctor Murray and doctor Miller

NOTE Confidence: 0.94478786

00:50:38.655 --> 00:50:40.415 actually worked on cascade screening

NOTE Confidence: 0.94478786

00:50:40.415 --> 00:50:41.715 for the New Haven population.

NOTE Confidence: 0.94478786

00:50:41.855 --> 00:50:43.215 That's why that's how we

NOTE Confidence: 0.94478786

00:50:43.215 --> 00:50:44.915 identify a subgroup of patients

NOTE Confidence: 0.8911907

00:50:45.295 --> 00:50:48.120 that have, genotype positive, phenotype,

NOTE Confidence: 0.9145177

00:50:48.739 --> 00:50:50.180 negative, and they're plugged into

NOTE Confidence: 0.9145177

00:50:50.180 --> 00:50:50.840 our clinic.

NOTE Confidence: 0.94392794

00:50:51.380 --> 00:50:52.920 We took that a notch,

NOTE Confidence: 0.74906516

00:50:53.460 --> 00:50:54.680 up with, do

NOTE Confidence: 0.9231348

00:50:55.060 --> 00:50:57.560 an educational grant on educating

NOTE Confidence: 0.87119323

00:50:58.020 --> 00:51:00.440 cascade screening carriers. And, like,

NOTE Confidence: 0.87119323

00:51:00.495 --> 00:51:00.735 the,

NOTE Confidence: 0.9623314

00:51:01.375 --> 00:51:02.895 the patients and their family

NOTE Confidence: 0.9623314

00:51:02.895 --> 00:51:04.415 that, have been identified to

NOTE Confidence: 0.9623314

00:51:04.415 --> 00:51:05.375 continue to do that in

NOTE Confidence: 0.9623314

00:51:05.375 --> 00:51:06.975 the community. So that's one

NOTE Confidence: 0.9623314

00:51:06.975 --> 00:51:07.455 thing.

NOTE Confidence: 0.9628669

00:51:07.775 --> 00:51:08.975 The second thing in terms

NOTE Confidence: 0.9628669

00:51:08.975 --> 00:51:09.715 of engaging

NOTE Confidence: 0.9701043

00:51:10.175 --> 00:51:11.375 those patients, you know, we

NOTE Confidence: 0.9701043

00:51:11.375 --> 00:51:11.855 know,

NOTE Confidence: 0.96837646

00:51:12.255 --> 00:51:14.260 with other manifestations of amyloid,

NOTE Confidence: 0.96837646

00:51:14.260 --> 00:51:15.299 like carpal tunnel. We know,

NOTE Confidence: 0.96837646

00:51:15.299 --> 00:51:17.000 for example, carpal tunnel happens

NOTE Confidence: 0.96837646

00:51:17.140 --> 00:51:18.500 about ten to fifteen years

NOTE Confidence: 0.96837646

00:51:18.500 --> 00:51:20.660 before it heart disease or

NOTE Confidence: 0.96837646

00:51:20.660 --> 00:51:22.900 amyloidosis becomes apparent. So we've

NOTE Confidence: 0.96837646

00:51:22.900 --> 00:51:24.180 leveraged that to bring it

NOTE Confidence: 0.96837646

00:51:24.180 --> 00:51:25.380 to the community. So there's

NOTE Confidence: 0.96837646

00:51:25.380 --> 00:51:26.579 a lot of relationships that

NOTE Confidence: 0.96837646

00:51:26.579 --> 00:51:27.994 we have with neurosurgery

NOTE Confidence: 0.9825747

00:51:28.375 --> 00:51:30.474 and ortho. For example, several

NOTE Confidence: 0.9825747

00:51:30.614 --> 00:51:31.755 colleagues from ortho,

NOTE Confidence: 0.9552939

00:51:32.055 --> 00:51:33.174 the time that they're doing

NOTE Confidence: 0.9552939

00:51:33.174 --> 00:51:35.094 their second carpal tunnel, are

NOTE Confidence: 0.9552939

00:51:35.094 --> 00:51:37.174 sending the biopsy and sending

NOTE Confidence: 0.9552939

00:51:37.174 --> 00:51:38.295 the patients to us. So,

NOTE Confidence: 0.9552939

00:51:38.295 --> 00:51:39.969 then, they're plugged in into

NOTE Confidence: 0.9552939

00:51:39.969 --> 00:51:40.930 the screening and then it

NOTE Confidence: 0.9552939

00:51:40.930 --> 00:51:42.630 takes us to your comment

NOTE Confidence: 0.9552939

00:51:42.770 --> 00:51:43.270 about

NOTE Confidence: 0.8913255

00:51:43.570 --> 00:51:44.550 are they truly

NOTE Confidence: 0.99919105

00:51:44.850 --> 00:51:45.350 symptomatic

NOTE Confidence: 0.8543815

00:51:45.730 --> 00:51:47.170 or not? And which is

NOTE Confidence: 0.8543815

00:51:47.170 --> 00:51:48.790 an excellent question.

NOTE Confidence: 0.9557389

00:51:49.570 --> 00:51:51.330 Sometimes we don't know and

NOTE Confidence: 0.9557389

00:51:51.330 --> 00:51:52.950 that's when CPET becomes,

NOTE Confidence: 0.9191677

00:51:53.330 --> 00:51:54.775 useful. You know, it's not

NOTE Confidence: 0.9191677

00:51:54.775 --> 00:51:56.535 that we always use CPET

NOTE Confidence: 0.9191677

00:51:56.535 --> 00:51:57.275 in particularly

NOTE Confidence: 0.9307785

00:51:57.815 --> 00:51:58.935 in those that are like

NOTE Confidence: 0.9307785

00:51:58.935 --> 00:52:00.395 twenty or thirty years,

NOTE Confidence: 0.9939142

00:52:00.775 --> 00:52:02.055 you know, different from that

NOTE Confidence: 0.9939142

00:52:02.055 --> 00:52:03.515 predicted age of onset.

NOTE Confidence: 0.9309632

00:52:04.055 --> 00:52:05.015 And the screening is a

NOTE Confidence: 0.9309632

00:52:05.015 --> 00:52:06.135 little bit different. For example,

NOTE Confidence: 0.9309632

00:52:06.135 --> 00:52:06.935 if I have a v

NOTE Confidence: 0.9309632

00:52:06.935 --> 00:52:08.609 one forty two I genetic

NOTE Confidence: 0.9309632

00:52:08.609 --> 00:52:10.289 screening that's like thirty versus

NOTE Confidence: 0.9309632

00:52:10.289 --> 00:52:12.130 someone like the patient who

NOTE Confidence: 0.9309632

00:52:12.130 --> 00:52:13.829 is like already sixty eight.

NOTE Confidence: 0.9302438

00:52:14.369 --> 00:52:15.569 So that kind of like

NOTE Confidence: 0.9302438

00:52:15.569 --> 00:52:17.009 ties into like, you know,

NOTE Confidence: 0.9302438

00:52:17.329 --> 00:52:18.609 the several questions in like

NOTE Confidence: 0.9302438

00:52:18.609 --> 00:52:20.049 the penetrance. Because obviously we're

NOTE Confidence: 0.9302438

00:52:20.049 --> 00:52:21.109 not gonna be doing,

NOTE Confidence: 0.97054255

00:52:21.569 --> 00:52:23.569 nuclear imaging or radiation patients

NOTE Confidence: 0.97054255

00:52:23.569 --> 00:52:25.145 that are thirty every, you

NOTE Confidence: 0.97054255

00:52:25.145 --> 00:52:26.925 know, three years and subjecting

NOTE Confidence: 0.97054255

00:52:27.065 --> 00:52:28.344 them for a disease that

NOTE Confidence: 0.97054255

00:52:28.344 --> 00:52:29.385 we know is gonna present

NOTE Confidence: 0.97054255

00:52:29.385 --> 00:52:30.605 twenty years from then.

NOTE Confidence: 0.90181863

00:52:34.984 --> 00:52:36.605 So, Sarah, so just,

NOTE Confidence: 0.9077659

00:52:37.145 --> 00:52:38.760 just congratulations on a wonderful

NOTE Confidence: 0.9077659

00:52:38.760 --> 00:52:40.280 talk, and I always it's

NOTE Confidence: 0.9077659

00:52:40.280 --> 00:52:41.800 a really a wonderful thing

NOTE Confidence: 0.9077659

00:52:41.800 --> 00:52:42.300 when,

NOTE Confidence: 0.96017575

00:52:42.840 --> 00:52:43.340 somebody,

NOTE Confidence: 0.93113595

00:52:44.120 --> 00:52:45.719 who's a mentee shows you

NOTE Confidence: 0.93113595

00:52:45.719 --> 00:52:46.620 things that you,

NOTE Confidence: 0.97362536

00:52:47.400 --> 00:52:49.480 stimulates new ideas and really

NOTE Confidence: 0.97362536

00:52:49.480 --> 00:52:50.380 takes the

NOTE Confidence: 0.93031144

00:52:50.984 --> 00:52:51.785 the the the knowledge to

NOTE Confidence: 0.93031144

00:52:51.785 --> 00:52:52.664 an to a new level.

NOTE Confidence: 0.93031144

00:52:52.664 --> 00:52:54.684 So congratulations on that. And,

NOTE Confidence: 0.9099734

00:52:55.384 --> 00:52:56.184 yeah, I think,

NOTE Confidence: 0.92129594

00:52:56.664 --> 00:52:57.704 a couple of, you know,

NOTE Confidence: 0.92129594

00:52:57.704 --> 00:52:58.505 sort of comments in that

NOTE Confidence: 0.92129594

00:52:58.505 --> 00:52:59.625 space and then a question.

NOTE Confidence: 0.92129594

00:52:59.625 --> 00:53:01.144 I think it is interesting

NOTE Confidence: 0.92129594

00:53:01.144 --> 00:53:02.265 to hear your their talk

NOTE Confidence: 0.92129594

00:53:02.265 --> 00:53:03.600 because when we started this,

NOTE Confidence: 0.92129594

00:53:03.840 --> 00:53:05.600 the mantra was everybody with

NOTE Confidence: 0.92129594

00:53:05.600 --> 00:53:07.040 half PEP should get a

NOTE Confidence: 0.92129594

00:53:07.040 --> 00:53:08.960 PYP or HMDP screen. And

NOTE Confidence: 0.92129594

00:53:08.960 --> 00:53:10.340 now we're moving that needle

NOTE Confidence: 0.92129594

00:53:10.400 --> 00:53:11.940 right to a different population

NOTE Confidence: 0.92129594

00:53:12.000 --> 00:53:12.900 of prevention.

NOTE Confidence: 0.9833804

00:53:13.600 --> 00:53:14.640 So I think that that's

NOTE Confidence: 0.9833804

00:53:14.640 --> 00:53:16.160 a that's a fantastic concept

NOTE Confidence: 0.9833804

00:53:16.160 --> 00:53:17.460 that we need to engender,

NOTE Confidence: 0.9578362

00:53:17.840 --> 00:53:18.320 across,

NOTE Confidence: 0.9994376

00:53:18.640 --> 00:53:19.575 all of our domains.

NOTE Confidence: 0.9667576

00:53:20.454 --> 00:53:21.734 And the second comment is

NOTE Confidence: 0.9667576

00:53:21.734 --> 00:53:22.234 about

NOTE Confidence: 0.80375165

00:53:22.535 --> 00:53:24.395 the ACT Early trial. And,

NOTE Confidence: 0.98737925

00:53:24.855 --> 00:53:26.454 Eric alluded to this, but

NOTE Confidence: 0.98737925

00:53:26.454 --> 00:53:28.135 think about this trial that

NOTE Confidence: 0.98737925

00:53:28.135 --> 00:53:30.075 a pharmaceutical company has been

NOTE Confidence: 0.98737925

00:53:30.135 --> 00:53:31.815 so courageous to support, which

NOTE Confidence: 0.98737925

00:53:31.815 --> 00:53:32.474 is basically,

NOTE Confidence: 0.95596284

00:53:33.290 --> 00:53:34.330 a trial that's looking at

NOTE Confidence: 0.95596284

00:53:34.330 --> 00:53:36.489 asymptomatic patients and treating them

NOTE Confidence: 0.95596284

00:53:36.489 --> 00:53:38.030 or randomizing them the treatment

NOTE Confidence: 0.9649229

00:53:38.330 --> 00:53:39.849 with no hope of really

NOTE Confidence: 0.9649229

00:53:39.849 --> 00:53:41.530 ever having an ROI. Right?

NOTE Confidence: 0.9649229

00:53:41.530 --> 00:53:43.050 Because that's gonna be the

NOTE Confidence: 0.9649229

00:53:43.050 --> 00:53:44.170 results from that are gonna

NOTE Confidence: 0.9649229

00:53:44.170 --> 00:53:45.530 be five years in the

NOTE Confidence: 0.9649229

00:53:45.530 --> 00:53:47.435 future and those but it's

NOTE Confidence: 0.9649229

00:53:47.435 --> 00:53:49.135 really a natural history study

NOTE Confidence: 0.9899992

00:53:49.594 --> 00:53:51.935 of TTR amyloidosis in asymptomatic

NOTE Confidence: 0.92331123

00:53:52.235 --> 00:53:53.515 gene carriers. So that's it

NOTE Confidence: 0.92331123

00:53:53.515 --> 00:53:54.655 can be just a phenomenal

NOTE Confidence: 0.92331123

00:53:54.715 --> 00:53:55.775 study to understand.

NOTE Confidence: 0.9592487

00:53:56.715 --> 00:53:57.675 And then my last my

NOTE Confidence: 0.9592487

00:53:57.675 --> 00:53:59.070 question for you really is

NOTE Confidence: 0.9592487

00:53:59.310 --> 00:54:00.430 incorporating all these all these

NOTE Confidence: 0.9592487

00:54:00.430 --> 00:54:02.210 concepts of prevention and therapeutics.

NOTE Confidence: 0.97055346

00:54:02.989 --> 00:54:04.590 How do you see the

NOTE Confidence: 0.97055346

00:54:04.590 --> 00:54:06.030 cost effectiveness? I know you

NOTE Confidence: 0.97055346

00:54:06.030 --> 00:54:06.910 didn't talk about this, but,

NOTE Confidence: 0.97055346

00:54:06.910 --> 00:54:07.870 like so how do you

NOTE Confidence: 0.97055346

00:54:07.870 --> 00:54:08.910 sort of see some of

NOTE Confidence: 0.97055346

00:54:08.910 --> 00:54:10.530 the some of those decisions

NOTE Confidence: 0.97055346

00:54:10.590 --> 00:54:11.890 or some of those modeling,

NOTE Confidence: 0.9892661

00:54:12.590 --> 00:54:14.030 playing out about the different

NOTE Confidence: 0.9892661

00:54:14.030 --> 00:54:16.244 therapies and and strategies that

NOTE Confidence: 0.9892661

00:54:16.244 --> 00:54:17.385 could be employed here?

NOTE Confidence: 0.97116226

00:54:18.005 --> 00:54:19.045 Well, I I think it's

NOTE Confidence: 0.97116226

00:54:19.045 --> 00:54:19.545 twofold.

NOTE Confidence: 0.97005284

00:54:20.165 --> 00:54:22.405 One big, like, disclaimer that

NOTE Confidence: 0.97005284

00:54:22.405 --> 00:54:23.684 I'm not the cost effective

NOTE Confidence: 0.97005284

00:54:23.684 --> 00:54:24.984 person in the room. But,

NOTE Confidence: 0.94799197

00:54:25.605 --> 00:54:26.984 two things. I think one,

NOTE Confidence: 0.94799197

00:54:27.045 --> 00:54:28.825 using AI is super scalable,

NOTE Confidence: 0.94799197

00:54:28.885 --> 00:54:29.920 very cheap. And I think

NOTE Confidence: 0.94799197

00:54:29.920 --> 00:54:31.200 this is demonstrated again and

NOTE Confidence: 0.94799197

00:54:31.200 --> 00:54:32.160 again that we can use

NOTE Confidence: 0.94799197

00:54:32.160 --> 00:54:33.600 it everywhere, especially with, like,

NOTE Confidence: 0.94799197

00:54:33.600 --> 00:54:34.180 the Ecolabs

NOTE Confidence: 0.96540576

00:54:34.560 --> 00:54:36.760 studies across the continents Mhmm.

NOTE Confidence: 0.96540576

00:54:36.960 --> 00:54:37.840 Of being it's such a

NOTE Confidence: 0.96540576

00:54:37.840 --> 00:54:39.040 scalable tool. So I think

NOTE Confidence: 0.96540576

00:54:39.040 --> 00:54:40.800 from a diagnostic perspective, I

NOTE Confidence: 0.96540576

00:54:40.800 --> 00:54:41.840 think it's not gonna be

NOTE Confidence: 0.96540576

00:54:41.840 --> 00:54:42.420 an issue,

NOTE Confidence: 0.94754267

00:54:43.040 --> 00:54:44.480 especially with the technology being

NOTE Confidence: 0.94754267

00:54:44.480 --> 00:54:46.025 so available even with single

NOTE Confidence: 0.94754267

00:54:46.025 --> 00:54:47.625 VP KJ's. And I think

NOTE Confidence: 0.94754267

00:54:47.625 --> 00:54:48.925 from a, you know,

NOTE Confidence: 0.995728

00:54:49.545 --> 00:54:50.525 treatment perspective,

NOTE Confidence: 0.9685802

00:54:50.825 --> 00:54:52.505 you know, we I've shown

NOTE Confidence: 0.9685802

00:54:52.505 --> 00:54:53.965 at least, like, two therapies,

NOTE Confidence: 0.9685802

00:54:54.025 --> 00:54:55.225 but I know that many

NOTE Confidence: 0.9685802

00:54:55.225 --> 00:54:56.665 and many and many are

NOTE Confidence: 0.9685802

00:54:56.665 --> 00:54:57.945 being developed. And I think

NOTE Confidence: 0.9685802

00:54:57.945 --> 00:54:59.705 that competition to, like, who

NOTE Confidence: 0.9685802

00:54:59.705 --> 00:55:00.205 develops

NOTE Confidence: 0.99009883

00:55:00.630 --> 00:55:01.750 the better drug is just

NOTE Confidence: 0.99009883

00:55:01.750 --> 00:55:02.950 gonna open the market for

NOTE Confidence: 0.99009883

00:55:02.950 --> 00:55:03.989 more and more drugs. And

NOTE Confidence: 0.99009883

00:55:03.989 --> 00:55:05.190 with more and more drugs

NOTE Confidence: 0.99009883

00:55:05.190 --> 00:55:07.109 available, I hope that people

NOTE Confidence: 0.99009883

00:55:07.109 --> 00:55:08.869 will, like, you know, start

NOTE Confidence: 0.99009883

00:55:08.869 --> 00:55:10.650 lowering the prices so that,

NOTE Confidence: 0.99009883

00:55:10.710 --> 00:55:11.910 you know, people actually use

NOTE Confidence: 0.99009883

00:55:11.910 --> 00:55:13.109 their drugs, and that would

NOTE Confidence: 0.99009883

00:55:13.109 --> 00:55:14.809 be, like, why, you know,

NOTE Confidence: 0.99009883

00:55:15.035 --> 00:55:16.075 people may tend to that.

NOTE Confidence: 0.99009883

00:55:16.075 --> 00:55:17.275 So I hope that that

NOTE Confidence: 0.99009883

00:55:17.275 --> 00:55:17.775 is,

NOTE Confidence: 0.9973443

00:55:18.475 --> 00:55:19.515 you know, what the future

NOTE Confidence: 0.9973443

00:55:19.515 --> 00:55:20.015 holds.

NOTE Confidence: 0.9692835

00:55:20.395 --> 00:55:21.114 Oh, yeah. I guess I

NOTE Confidence: 0.9692835

00:55:21.114 --> 00:55:22.395 should edit my comments because

NOTE Confidence: 0.9692835

00:55:22.395 --> 00:55:23.515 this is recorded, and it's

NOTE Confidence: 0.9692835

00:55:23.515 --> 00:55:24.475 totally gonna have a good

NOTE Confidence: 0.9692835

00:55:24.475 --> 00:55:25.915 ROI. BridgeBio, it's gonna give

NOTE Confidence: 0.9692835

00:55:25.915 --> 00:55:26.735 a great ROI.

NOTE Confidence: 0.97603166

00:55:33.239 --> 00:55:35.160 Sarah, that that was a

NOTE Confidence: 0.97603166

00:55:35.160 --> 00:55:36.299 very professorial

NOTE Confidence: 0.9807715

00:55:37.239 --> 00:55:39.079 presentation, so I'll call you

NOTE Confidence: 0.9807715

00:55:39.079 --> 00:55:40.700 professor at least for this

NOTE Confidence: 0.9807715

00:55:40.920 --> 00:55:42.059 for this hour.

NOTE Confidence: 0.98211503

00:55:43.395 --> 00:55:44.995 So, you know, maybe following

NOTE Confidence: 0.98211503

00:55:44.995 --> 00:55:45.795 up a little bit on

NOTE Confidence: 0.98211503

00:55:45.795 --> 00:55:47.015 some of the other comments,

NOTE Confidence: 0.98211503

00:55:47.075 --> 00:55:48.135 I think early

NOTE Confidence: 0.99939746

00:55:48.915 --> 00:55:50.695 treatment of asymptomatic

NOTE Confidence: 0.9997695

00:55:51.315 --> 00:55:51.815 individuals

NOTE Confidence: 0.984138

00:55:52.195 --> 00:55:53.735 in any disease state

NOTE Confidence: 0.9777024

00:55:54.114 --> 00:55:55.175 is going to

NOTE Confidence: 0.8591698

00:55:55.719 --> 00:55:57.020 our our enthusiasm

NOTE Confidence: 0.98328435

00:55:57.320 --> 00:55:58.360 for that is going to

NOTE Confidence: 0.98328435

00:55:58.360 --> 00:56:00.300 depend on the risk benefit

NOTE Confidence: 0.7611623

00:56:01.160 --> 00:56:01.660 ratio,

NOTE Confidence: 0.9771619

00:56:02.040 --> 00:56:03.260 essentially, or analysis.

NOTE Confidence: 0.9740896

00:56:03.800 --> 00:56:05.320 And so that kind of

NOTE Confidence: 0.9740896

00:56:05.320 --> 00:56:06.700 loops me to the CRISPR

NOTE Confidence: 0.57268393

00:56:07.000 --> 00:56:07.500 Cas9

NOTE Confidence: 0.9482049

00:56:08.525 --> 00:56:09.665 story where,

NOTE Confidence: 0.9949756

00:56:10.045 --> 00:56:11.805 you know, gene editing is

NOTE Confidence: 0.9949756

00:56:11.805 --> 00:56:13.025 potentially curative.

NOTE Confidence: 0.9961606

00:56:13.325 --> 00:56:13.825 Right?

NOTE Confidence: 0.99693835

00:56:14.205 --> 00:56:14.705 And

NOTE Confidence: 0.9772122

00:56:15.005 --> 00:56:17.085 the issue there, I think

NOTE Confidence: 0.9772122

00:56:17.085 --> 00:56:18.844 the biggest concern with that

NOTE Confidence: 0.9772122

00:56:18.844 --> 00:56:20.364 kind of gene editing is

NOTE Confidence: 0.9772122

00:56:20.364 --> 00:56:20.864 specificity

NOTE Confidence: 0.9671628

00:56:21.165 --> 00:56:22.844 and off target gene off

NOTE Confidence: 0.9671628

00:56:22.844 --> 00:56:23.745 target effects.

NOTE Confidence: 0.9358515

00:56:24.420 --> 00:56:26.020 So I'm my question is

NOTE Confidence: 0.9358515

00:56:26.020 --> 00:56:27.380 in the studies that you

NOTE Confidence: 0.9358515

00:56:27.380 --> 00:56:27.880 mentioned,

NOTE Confidence: 0.9992675

00:56:28.660 --> 00:56:30.180 do you know how many

NOTE Confidence: 0.9992675

00:56:30.180 --> 00:56:30.680 different

NOTE Confidence: 0.97635955

00:56:31.380 --> 00:56:33.239 genetic variants were tested?

NOTE Confidence: 0.9869172

00:56:33.619 --> 00:56:35.140 Because it's not one guide

NOTE Confidence: 0.9869172

00:56:35.140 --> 00:56:36.579 fits all. Right? It's gonna

NOTE Confidence: 0.9869172

00:56:36.579 --> 00:56:38.099 be different guides for different

NOTE Confidence: 0.9869172

00:56:38.099 --> 00:56:39.319 targets of the gene

NOTE Confidence: 0.9998202

00:56:39.885 --> 00:56:40.385 that

NOTE Confidence: 0.9006555

00:56:40.685 --> 00:56:41.425 are variant.

NOTE Confidence: 0.98788863

00:56:41.965 --> 00:56:43.485 And some are probably gonna

NOTE Confidence: 0.98788863

00:56:43.485 --> 00:56:45.165 work very well, be very

NOTE Confidence: 0.98788863

00:56:45.165 --> 00:56:47.005 specific, have no off target

NOTE Confidence: 0.98788863

00:56:47.005 --> 00:56:49.325 effects, and some won't be

NOTE Confidence: 0.98788863

00:56:49.325 --> 00:56:51.485 like that. So it those

NOTE Confidence: 0.98788863

00:56:51.485 --> 00:56:53.085 published studies, did they test

NOTE Confidence: 0.98788863

00:56:53.085 --> 00:56:54.364 a bunch of different variants,

NOTE Confidence: 0.98788863

00:56:54.364 --> 00:56:55.599 or was it did they

NOTE Confidence: 0.98788863

00:56:55.599 --> 00:56:56.500 focus on

NOTE Confidence: 0.9459226

00:56:56.800 --> 00:56:57.760 on one? Thank you so

NOTE Confidence: 0.9459226

00:56:57.760 --> 00:56:59.040 much, doctor Bender. This is

NOTE Confidence: 0.9459226

00:56:59.040 --> 00:57:00.560 such a great Profession. Coming

NOTE Confidence: 0.9459226

00:57:00.560 --> 00:57:01.200 from you. But,

NOTE Confidence: 0.94116145

00:57:01.680 --> 00:57:02.719 I actually don't know the

NOTE Confidence: 0.94116145

00:57:02.719 --> 00:57:04.160 answer because I mostly looked

NOTE Confidence: 0.94116145

00:57:04.160 --> 00:57:05.359 at the clinical studies. So

NOTE Confidence: 0.94116145

00:57:05.359 --> 00:57:06.079 I don't know in the

NOTE Confidence: 0.94116145

00:57:06.079 --> 00:57:07.855 preclinical setting, like, how many

NOTE Confidence: 0.94116145

00:57:07.855 --> 00:57:09.535 guides they actually tested on

NOTE Confidence: 0.94116145

00:57:09.535 --> 00:57:10.735 in animal models and some

NOTE Confidence: 0.94116145

00:57:10.735 --> 00:57:11.535 ways. But I can definitely

NOTE Confidence: 0.94116145

00:57:11.535 --> 00:57:12.415 look into that and get

NOTE Confidence: 0.94116145

00:57:12.415 --> 00:57:14.094 back to them. Okay. Yep.

NOTE Confidence: 0.94116145

00:57:14.094 --> 00:57:15.635 Fair enough. Actually,

NOTE Confidence: 0.87727886

00:57:16.095 --> 00:57:17.375 you are I don't know.

NOTE Confidence: 0.87727886

00:57:17.375 --> 00:57:18.035 I'm done.

NOTE Confidence: 0.8721954

00:57:20.440 --> 00:57:21.480 Actually, you asked the same

NOTE Confidence: 0.8721954

00:57:21.480 --> 00:57:23.080 question but not not in

NOTE Confidence: 0.8721954

00:57:23.080 --> 00:57:24.540 this in that format because,

NOTE Confidence: 0.85472363

00:57:24.840 --> 00:57:26.360 actually, this is more CRISPR

NOTE Confidence: 0.85472363

00:57:26.360 --> 00:57:27.180 cast knockout.

NOTE Confidence: 0.94259804

00:57:27.640 --> 00:57:28.520 So it doesn't matter what

NOTE Confidence: 0.94259804

00:57:28.520 --> 00:57:29.800 mutation you have. They actually

NOTE Confidence: 0.94259804

00:57:29.800 --> 00:57:31.160 target the whole gene. Yeah.

NOTE Confidence: 0.94259804

00:57:31.160 --> 00:57:31.960 So even if you have

NOTE Confidence: 0.94259804

00:57:31.960 --> 00:57:33.480 variants yeah. This is not

NOTE Confidence: 0.94259804

00:57:33.480 --> 00:57:34.825 the this is not gonna

NOTE Confidence: 0.94259804

00:57:34.825 --> 00:57:36.685 be correction of your, variant.

NOTE Confidence: 0.94259804

00:57:36.825 --> 00:57:38.025 So it it they have

NOTE Confidence: 0.94259804

00:57:38.025 --> 00:57:39.785 done every different type many

NOTE Confidence: 0.94259804

00:57:39.785 --> 00:57:41.645 different types. But my question,

NOTE Confidence: 0.91465074

00:57:42.025 --> 00:57:43.945 obviously, what Jeff mentioned is

NOTE Confidence: 0.91465074

00:57:43.945 --> 00:57:45.225 obviously a concern that the

NOTE Confidence: 0.91465074

00:57:45.225 --> 00:57:46.585 off target effect still can

NOTE Confidence: 0.91465074

00:57:46.585 --> 00:57:47.070 be there.

NOTE Confidence: 0.988507

00:57:47.630 --> 00:57:48.750 And that has been kind

NOTE Confidence: 0.988507

00:57:48.750 --> 00:57:50.030 of causing problem with other

NOTE Confidence: 0.988507

00:57:50.030 --> 00:57:50.910 CRISPRs. I don't know how

NOTE Confidence: 0.988507

00:57:50.910 --> 00:57:51.710 much you know about that

NOTE Confidence: 0.988507

00:57:51.710 --> 00:57:52.610 in this area.

NOTE Confidence: 0.97877425

00:57:53.070 --> 00:57:54.350 That was one question. And

NOTE Confidence: 0.97877425

00:57:54.350 --> 00:57:56.030 the second is that you

NOTE Confidence: 0.97877425

00:57:56.030 --> 00:57:58.110 mentioned, which is correct, that

NOTE Confidence: 0.97877425

00:57:58.110 --> 00:57:59.230 we have to always use

NOTE Confidence: 0.97877425

00:57:59.230 --> 00:57:59.710 light chain

NOTE Confidence: 0.9550756

00:58:00.350 --> 00:58:01.890 rule out light chain first.

NOTE Confidence: 0.9773613

00:58:02.190 --> 00:58:03.444 But we often see people

NOTE Confidence: 0.9773613

00:58:03.444 --> 00:58:05.125 coming from outside hospital with

NOTE Confidence: 0.9773613

00:58:05.125 --> 00:58:06.345 the PYP scan

NOTE Confidence: 0.80429184

00:58:07.125 --> 00:58:07.625 positive.

NOTE Confidence: 0.9639665

00:58:08.165 --> 00:58:09.785 How often are they falsely

NOTE Confidence: 0.9639665

00:58:09.845 --> 00:58:11.765 positive that this pathway has

NOTE Confidence: 0.9639665

00:58:11.765 --> 00:58:13.785 to be kind of regarded

NOTE Confidence: 0.9639665

00:58:13.845 --> 00:58:15.045 and say, okay. You should

NOTE Confidence: 0.9639665

00:58:15.045 --> 00:58:16.585 have done the first AL,

NOTE Confidence: 0.9639665

00:58:16.780 --> 00:58:17.820 then come to me as

NOTE Confidence: 0.9639665

00:58:17.820 --> 00:58:19.260 a cardiac. How often do

NOTE Confidence: 0.9639665

00:58:19.260 --> 00:58:20.860 you have false positive? Yeah.

NOTE Confidence: 0.9639665

00:58:20.860 --> 00:58:21.740 So I think that's a

NOTE Confidence: 0.9639665

00:58:21.740 --> 00:58:23.340 great question, and I think

NOTE Confidence: 0.9639665

00:58:23.340 --> 00:58:24.620 I personally had that with

NOTE Confidence: 0.9639665

00:58:24.620 --> 00:58:25.980 many of my patients, so

NOTE Confidence: 0.9639665

00:58:25.980 --> 00:58:27.580 they actually can be, like,

NOTE Confidence: 0.9639665

00:58:27.580 --> 00:58:28.800 have both diseases.

NOTE Confidence: 0.9856969

00:58:29.740 --> 00:58:31.135 The frequency, I don't know

NOTE Confidence: 0.9856969

00:58:31.135 --> 00:58:31.855 off the top of my

NOTE Confidence: 0.9856969

00:58:31.855 --> 00:58:33.075 head, but it's not insignificant.

NOTE Confidence: 0.90138227

00:58:33.695 --> 00:58:35.475 And and the guideline recommendations,

NOTE Confidence: 0.998372

00:58:35.775 --> 00:58:36.275 technically

NOTE Confidence: 0.9728236

00:58:36.655 --> 00:58:38.675 technically speaking, the guideline recommendations

NOTE Confidence: 0.9728236

00:58:38.735 --> 00:58:40.255 is rule AL out first

NOTE Confidence: 0.9728236

00:58:40.415 --> 00:58:41.955 Right. Then test for TTR,

NOTE Confidence: 0.9728236

00:58:42.015 --> 00:58:43.215 but most people do it

NOTE Confidence: 0.9728236

00:58:43.215 --> 00:58:43.715 simultaneously.

NOTE Confidence: 0.99466

00:58:44.580 --> 00:58:45.380 But but I do think

NOTE Confidence: 0.99466

00:58:45.380 --> 00:58:46.740 it's important, like, from a

NOTE Confidence: 0.99466

00:58:46.740 --> 00:58:47.780 clinical perspective to do I

NOTE Confidence: 0.99466

00:58:47.780 --> 00:58:48.420 don't know if you have

NOTE Confidence: 0.99466

00:58:48.420 --> 00:58:49.480 an exact number.

NOTE Confidence: 0.98055136

00:58:53.940 --> 00:58:55.140 Yeah. The the rate of

NOTE Confidence: 0.98055136

00:58:55.140 --> 00:58:56.655 MGUS, which is what we're

NOTE Confidence: 0.98055136

00:58:56.895 --> 00:58:58.095 usually concerned about in this

NOTE Confidence: 0.98055136

00:58:58.095 --> 00:58:59.615 population, is between fifteen and

NOTE Confidence: 0.98055136

00:58:59.615 --> 00:59:00.895 twenty percent of all patients

NOTE Confidence: 0.98055136

00:59:00.895 --> 00:59:02.255 who are referred for TTR,

NOTE Confidence: 0.98055136

00:59:02.255 --> 00:59:04.575 which is which we do

NOTE Confidence: 0.98055136

00:59:04.655 --> 00:59:06.575 or we're meticulous about tracking

NOTE Confidence: 0.98055136

00:59:06.575 --> 00:59:08.095 down those results and repeating

NOTE Confidence: 0.98055136

00:59:08.095 --> 00:59:08.595 them,

NOTE Confidence: 0.991681

00:59:09.290 --> 00:59:10.570 and it prompts a lot

NOTE Confidence: 0.991681

00:59:10.570 --> 00:59:12.430 of referrals to our hematology

NOTE Confidence: 0.991681

00:59:12.570 --> 00:59:13.710 colleagues, and it also,

NOTE Confidence: 0.99058723

00:59:14.410 --> 00:59:16.330 speaks to the expertise of

NOTE Confidence: 0.99058723

00:59:16.330 --> 00:59:18.270 our center because we have,

NOTE Confidence: 0.9767939

00:59:18.970 --> 00:59:20.410 the ability to do to

NOTE Confidence: 0.9767939

00:59:20.410 --> 00:59:22.490 do, endomyocardial biopsies on native

NOTE Confidence: 0.9767939

00:59:22.490 --> 00:59:23.450 hearts. And that's a really

NOTE Confidence: 0.9767939

00:59:23.450 --> 00:59:25.395 key aspect of of our

NOTE Confidence: 0.9767939

00:59:25.395 --> 00:59:27.095 program to ensure that we're

NOTE Confidence: 0.9767939

00:59:27.155 --> 00:59:27.655 we're,

NOTE Confidence: 0.9968154

00:59:28.675 --> 00:59:29.175 maximizing

NOTE Confidence: 0.9993469

00:59:29.475 --> 00:59:31.415 specificity in those complex patients.

NOTE Confidence: 0.9874262

00:59:33.155 --> 00:59:34.435 And to answer your second

NOTE Confidence: 0.9874262

00:59:34.435 --> 00:59:35.875 question, I don't know about

NOTE Confidence: 0.9874262

00:59:35.875 --> 00:59:37.095 the off target effect.

NOTE Confidence: 0.92677665

00:59:43.150 --> 00:59:44.990 TTR and, like, crossing the

NOTE Confidence: 0.92677665

00:59:44.990 --> 00:59:46.849 blood pressure barrier and also

NOTE Confidence: 0.92677665

00:59:47.069 --> 00:59:48.589 the effect of, like, lowering

NOTE Confidence: 0.92677665

00:59:48.589 --> 00:59:49.890 the overall TTR

NOTE Confidence: 0.92538553

00:59:50.269 --> 00:59:52.109 to to transport, you know,

NOTE Confidence: 0.92538553

00:59:52.109 --> 00:59:54.190 thyroxine and but we don't

NOTE Confidence: 0.92538553

00:59:54.190 --> 00:59:55.825 know because these, you know,

NOTE Confidence: 0.92538553

00:59:55.825 --> 00:59:57.025 we probably need to wait,

NOTE Confidence: 0.92538553

00:59:57.025 --> 00:59:58.065 like, a decade or so

NOTE Confidence: 0.92538553

00:59:58.065 --> 00:59:59.665 to see, like, those potential

NOTE Confidence: 0.92538553

00:59:59.665 --> 01:00:00.405 of targets.

NOTE Confidence: 0.97227675

01:00:02.225 --> 01:00:03.925 Perfect. Well, thank you everyone

NOTE Confidence: 0.97227675

01:00:03.985 --> 01:00:05.105 for being here today. I

NOTE Confidence: 0.97227675

01:00:05.105 --> 01:00:06.645 really appreciate it. Thank you.