WEBVTT

NOTE duration:"00:55:43.3200000"

NOTE recognizability:0.789

NOTE language:en-us

NOTE Confidence: 0.13627322

00:00:10.720 --> 00:00:11.120 Yes,

NOTE Confidence: 0.430675045

00:00:22.840 --> 00:00:24.120 I'm just trying to give it back too.

NOTE Confidence: 0.430675045

00:00:24.120 --> 00:00:27.354 So at the end, I have questions

NOTE Confidence: 0.430675045

00:00:27.360 --> 00:00:29.460 and there's just about online that

NOTE Confidence: 0.430675045

00:00:29.460 --> 00:00:31.320 I'll get the questions too. But,

NOTE Confidence: 0.51757326

00:00:35.840 --> 00:00:38.640 but I'm going to pop down and

NOTE Confidence: 0.51757326

00:00:38.640 --> 00:00:40.960 I'm going to go through. OK,

NOTE Confidence: 0.946008966666667

00:00:53.320 --> 00:00:54.598 good afternoon, everybody.

NOTE Confidence: 0.8572224775

00:00:54.800 --> 00:00:55.856 We'll get started.

NOTE Confidence: 0.8572224775

00:00:55.856 --> 00:00:57.616 Welcome to Grand Rounds in

NOTE Confidence: 0.8572224775

00:00:57.616 --> 00:00:59.199 the Department of Pediatrics.

NOTE Confidence: 0.8572224775

00:00:59.200 --> 00:01:00.280 My name is Cliff Bogue.

NOTE Confidence: 0.8572224775

00:01:00.280 --> 00:01:02.156 I'm the chair of the department and

NOTE Confidence: 0.8572224775

00:01:02.156 --> 00:01:04.660 pleased to have all of you here and

NOTE Confidence: 0.8572224775

00:01:04.660 --> 00:01:06.360 especially our special guest speaker.

NOTE Confidence: 0.8572224775

00:01:06.360 --> 00:01:08.138 So I just have a few announcements

NOTE Confidence: 0.8572224775

00:01:08.138 --> 00:01:09.330 beforehand and then I'm going

NOTE Confidence: 0.8572224775

00:01:09.330 --> 00:01:12.196 to turn it over to Young *****

NOTE Confidence: 0.8572224775

00:01:12.200 --> 00:01:14.044 to introduce today's speaker.

NOTE Confidence: 0.8572224775

00:01:14.044 --> 00:01:17.260 So our upcoming next two grand rounds

NOTE Confidence: 0.8572224775

00:01:17.260 --> 00:01:20.212 next week we have what we call cared

NOTE Confidence: 0.8572224775

00:01:20.212 --> 00:01:22.712 care rounds and this is talking

NOTE Confidence: 0.8572224775

00:01:22.712 --> 00:01:24.702 about collateral damage orphaned by

NOTE Confidence: 0.8572224775

00:01:24.702 --> 00:01:27.506 trauma and we have Matthew Hornick

NOTE Confidence: 0.8572224775

00:01:27.506 --> 00:01:30.570 in peed surgery as long as Jessica

NOTE Confidence: 0.8572224775

00:01:30.570 --> 00:01:33.410 and Heather who are going to be here

NOTE Confidence: 0.8572224775

00:01:33.410 --> 00:01:36.088 to talk about a case presentation.

NOTE Confidence: 0.8572224775

00:01:36.088 --> 00:01:38.488 And then the next week,

NOTE Confidence: 0.8572224775

00:01:38.488 --> 00:01:39.320 April 17th,

NOTE Confidence: 0.8572224775

00:01:39.320 --> 00:01:41.180 we have Kristen Schroeder who's

NOTE Confidence: 0.8572224775

00:01:41.180 --> 00:01:43.544 coming from Duke University to talk

NOTE Confidence: 0.8572224775

00:01:43.544 --> 00:01:45.320 about global oncology development

NOTE Confidence: 0.8572224775

00:01:45.320 --> 00:01:47.096 of a comprehensive pediatric

NOTE Confidence: 0.8572224775

00:01:47.096 --> 00:01:48.800 cancer program in Tanzania.

NOTE Confidence: 0.8572224775

00:01:48.800 --> 00:01:52.520 So that should be really interesting.

NOTE Confidence: 0.8572224775

00:01:52.520 --> 00:01:54.336 Also for those of you who are going

NOTE Confidence: 0.8572224775

00:01:54.336 --> 00:01:56.358 to the pediatric academic societies

NOTE Confidence: 0.916496578

00:01:56.360 --> 00:01:57.600 meeting in a few weeks,

NOTE Confidence: 0.852377652222222

00:01:58.520 --> 00:02:00.584 please come out on Saturday night

NOTE Confidence: 0.852377652222222

00:02:00.584 --> 00:02:02.588 to our dessert reception will be

NOTE Confidence: 0.852377652222222

00:02:02.588 --> 00:02:04.280 at the Fairmont Royal York at.

NOTE Confidence: 0.852377652222222

00:02:04.280 --> 00:02:06.760 You're welcome. Bring your friends,

NOTE Confidence: 0.852377652222222

00:02:06.760 --> 00:02:08.240 people that you know alumni.

NOTE Confidence: 0.852377652222222

00:02:08.240 --> 00:02:10.224 We'd love to see folks and have a

NOTE Confidence: 0.852377652222222

00:02:10.224 --> 00:02:12.100 chance to connect and enjoy one

NOTE Confidence: 0.852377652222222

00:02:12.100 --> 00:02:14.074 another at that meeting in Toronto.

NOTE Confidence: 0.919692112173913

00:02:16.240 --> 00:02:19.381 Also we have, as you know we're getting near

NOTE Confidence: 0.919692112173913

00:02:19.381 --> 00:02:22.337 the end of our strategic planning process

NOTE Confidence: 0.919692112173913

00:02:22.337 --> 00:02:25.478 that's been going on for several months.

NOTE Confidence: 0.919692112173913

00:02:25.480 --> 00:02:28.343 We're going to have a several one

NOTE Confidence: 0.919692112173913

00:02:28.343 --> 00:02:30.550 hour virtual strategic plan feedback

NOTE Confidence: 0.919692112173913

00:02:30.550 --> 00:02:33.402 sessions as an opportunity to give some

NOTE Confidence: 0.919692112173913

00:02:33.402 --> 00:02:34.907 final feedback and most importantly

NOTE Confidence: 0.919692112173913

00:02:34.907 --> 00:02:36.798 think about how do we move forward,

NOTE Confidence: 0.919692112173913

00:02:36.800 --> 00:02:39.502 how do we get a broad buy in for some of the

NOTE Confidence: 0.919692112173913

00:02:39.502 --> 00:02:41.880 exciting things we have in the in the plan.

NOTE Confidence: 0.919692112173913

00:02:41.880 --> 00:02:43.924 So you'll be these

NOTE Confidence: 0.919692112173913

00:02:43.924 --> 00:02:46.479 invitations will be going out,

NOTE Confidence: 0.919692112173913

00:02:46.480 --> 00:02:49.729 but you can see we have them focused in

NOTE Confidence: 0.919692112173913

00:02:49.729 --> 00:02:52.800 various pillars of of our department and

NOTE Confidence: 0.919692112173913

00:02:52.800 --> 00:02:56.160 and so please encourage you if you're

NOTE Confidence: 0.919692112173913

00:02:56.160 --> 00:02:59.480 available come to those and participate.

NOTE Confidence: 0.919692112173913

00:02:59.480 --> 00:03:01.916 They'll be really one of the last

NOTE Confidence: 0.919692112173913

00:03:01.916 --> 00:03:04.075 chances for that kind of impact

NOTE Confidence: 0.919692112173913

00:03:04.075 --> 00:03:06.444 input before we sort of finalize the

NOTE Confidence: 0.919692112173913

00:03:06.444 --> 00:03:08.680 plan and then begin to implement it.

NOTE Confidence: 0.919692112173913

00:03:08.680 --> 00:03:11.348 All of our grand rounds are

NOTE Confidence: 0.919692112173913

00:03:11.348 --> 00:03:12.752 available for CME.

NOTE Confidence: 0.919692112173913

00:03:12.752 --> 00:03:15.560 We don't have any commercial support.

NOTE Confidence: 0.919692112173913

00:03:15.560 --> 00:03:17.713 The number to text is here in

NOTE Confidence: 0.919692112173913

00:03:17.713 --> 00:03:19.478 good old whiteboard and also

NOTE Confidence: 0.919692112173913

00:03:19.478 --> 00:03:21.720 we'll be in the Zoom chat,

NOTE Confidence: 0.919692112173913

00:03:21.720 --> 00:03:25.026 but you can get CME credit

NOTE Confidence: 0.919692112173913

00:03:25.026 --> 00:03:26.679 for participation today.

NOTE Confidence: 0.919692112173913

00:03:26.680 --> 00:03:27.364 And with that,

NOTE Confidence: 0.919692112173913

00:03:27.364 --> 00:03:29.331 I'm going to turn it over to Yang

NOTE Confidence: 0.919692112173913

00:03:29.331 --> 00:03:31.197 Hui from the Department of Genetics,

NOTE Confidence: 0.919692112173913

00:03:31.200 --> 00:03:34.434 but also a close colleague in Pediatrics

NOTE Confidence: 0.919692112173913

00:03:34.440 --> 00:03:35.800 to introduce today's speaker.

NOTE Confidence: 0.7279423

00:03:39.280 --> 00:03:41.640 Thank you, Cliff. Indeed,

NOTE Confidence: 0.819277502307692

00:03:41.640 --> 00:03:44.209 I'm the professor for genetics and Pediatrics

NOTE Confidence: 0.819277502307692

00:03:44.209 --> 00:03:48.080 and Chief for the clinical genetics service.

NOTE Confidence: 0.819277502307692

00:03:48.080 --> 00:03:50.068 Since last year we started in this

NOTE Confidence: 0.819277502307692

00:03:50.068 --> 00:03:51.440 called the pediatric genetics,

NOTE Confidence: 0.819277502307692

00:03:51.440 --> 00:03:54.032 joined Ron and last year was a great success.

NOTE Confidence: 0.819277502307692

00:03:54.040 --> 00:03:55.818 And then we're going to keep doing

NOTE Confidence: 0.819277502307692

00:03:55.818 --> 00:03:57.558 that every year and hope maybe we'll

NOTE Confidence: 0.819277502307692

00:03:57.558 --> 00:04:01.678 do more and then one time per year

NOTE Confidence: 0.819277502307692

00:04:01.680 --> 00:04:04.236 today is the best special speaker.

NOTE Confidence: 0.819277502307692

00:04:04.240 --> 00:04:06.808 It's my prefer to kind of

NOTE Confidence: 0.819277502307692

00:04:06.808 --> 00:04:09.680 introduce Doctor William GAO.

NOTE Confidence: 0.819277502307692

00:04:09.680 --> 00:04:10.640 We should call Beer GAO.

NOTE Confidence: 0.819277502307692

00:04:10.640 --> 00:04:12.599 It's much easier.

NOTE Confidence: 0.819277502307692

00:04:12.600 --> 00:04:15.678 So for the people like Beer

NOTE Confidence: 0.819277502307692

00:04:15.680 --> 00:04:18.560 clearly take a lecture to tell

NOTE Confidence: 0.819277502307692

00:04:18.560 --> 00:04:21.146 his career great career for sure.

NOTE Confidence: 0.819277502307692

00:04:21.146 --> 00:04:25.375 I can spend our to talking to the

NOTE Confidence: 0.819277502307692

00:04:25.375 --> 00:04:27.880 his career or he can tell the story.

NOTE Confidence: 0.819277502307692

00:04:27.880 --> 00:04:28.760 Bill is good storyteller.

NOTE Confidence: 0.819277502307692

00:04:28.760 --> 00:04:31.936 He said OK I can tell story all the time.

NOTE Confidence: 0.819277502307692

00:04:31.936 --> 00:04:34.292 So very quickly some is on the fly

NOTE Confidence: 0.819277502307692

00:04:34.292 --> 00:04:36.626 this introduction for that and which

NOTE Confidence: 0.819277502307692

00:04:36.626 --> 00:04:38.480 very quickly highlight something.

NOTE Confidence: 0.819277502307692

00:04:38.480 --> 00:04:40.256 I will not touch UDMUDP because

NOTE Confidence: 0.819277502307692

00:04:40.256 --> 00:04:42.329 he's going to tell the story just

NOTE Confidence: 0.819277502307692

00:04:42.329 --> 00:04:44.063 put more not in the description

NOTE Confidence: 0.819277502307692

00:04:44.063 --> 00:04:46.038 in the fly a few highlights.

NOTE Confidence: 0.819277502307692

00:04:46.040 --> 00:04:50.142 So Bill Current is a senior

NOTE Confidence: 0.819277502307692

00:04:50.142 --> 00:04:52.674 investigator and the director for UDP,

NOTE Confidence: 0.819277502307692

00:04:52.680 --> 00:04:55.278 the head of a biochemical genetics.

NOTE Confidence: 0.819277502307692

00:04:55.280 --> 00:04:58.352 He usually said he given a lot of

NOTE Confidence: 0.819277502307692

00:04:58.352 --> 00:05:01.100 title last maybe 10 years and then

NOTE Confidence: 0.819277502307692

00:05:01.100 --> 00:05:04.150 he was the clinical director for the

NOTE Confidence: 0.819277502307692

00:05:04.150 --> 00:05:07.078 NHGI for almost longer than 15 years.

NOTE Confidence: 0.819277502307692

00:05:07.080 --> 00:05:09.243 A long very very long than many

NOTE Confidence: 0.819277502307692

00:05:09.243 --> 00:05:10.600 other title section chief.

NOTE Confidence: 0.819277502307692

00:05:10.600 --> 00:05:13.918 Also he declined a lot of exciting

NOTE Confidence: 0.819277502307692

00:05:13.918 --> 00:05:17.574 offer to he could be the and I and

NOTE Confidence: 0.819277502307692

00:05:17.574 --> 00:05:19.362 I see actually director at some

NOTE Confidence: 0.819277502307692

00:05:19.362 --> 00:05:21.905 point he said I don't want that one

NOTE Confidence: 0.819277502307692

00:05:21.905 --> 00:05:23.967 or department chair some school and

NOTE Confidence: 0.819277502307692

00:05:23.967 --> 00:05:26.690 all together but he clearly want to

NOTE Confidence: 0.819277502307692

00:05:26.690 --> 00:05:29.820 dedicate his time to working on rare

NOTE Confidence: 0.819277502307692

00:05:29.820 --> 00:05:31.900 disease undiagnosed disease that's

NOTE Confidence: 0.819277502307692

00:05:31.900 --> 00:05:35.559 what he's the signature program he created.

NOTE Confidence: 0.819277502307692

00:05:35.560 --> 00:05:38.608 He's a funding director 2008 and

NOTE Confidence: 0.819277502307692

00:05:38.608 --> 00:05:42.396 that led to the UDN Undiagnosed

NOTE Confidence: 0.819277502307692

00:05:42.396 --> 00:05:44.560 Disease Network 2017 right

NOTE Confidence: 0.782711955

00:05:46.960 --> 00:05:48.380 2017. Now he remained

NOTE Confidence: 0.782711955

00:05:48.380 --> 00:05:49.800 active for that program.

NOTE Confidence: 0.782711955

00:05:49.800 --> 00:05:52.120 He gave up many titles but he keep

NOTE Confidence: 0.782711955

00:05:52.120 --> 00:05:55.950 this one for long term so quickly

NOTE Confidence: 0.782711955

00:05:55.950 --> 00:06:00.243 be a graduate from MIT and then it

NOTE Confidence: 0.782711955

00:06:00.243 --> 00:06:01.855 was probably missing opportunity

NOTE Confidence: 0.782711955

00:06:01.855 --> 00:06:04.915 for Harvard did not take him to the

NOTE Confidence: 0.782711955

00:06:04.915 --> 00:06:06.853 Harvard Medical School and he went

NOTE Confidence: 0.782711955

00:06:06.853 --> 00:06:09.428 to the Wisconsin finished MDPHD and

NOTE Confidence: 0.782711955

00:06:09.428 --> 00:06:12.480 did a pediatric residency and he was

NOTE Confidence: 0.782711955

00:06:12.564 --> 00:06:16.060 a chief resident and and also come to

NOTE Confidence: 0.782711955

00:06:16.060 --> 00:06:18.866 the NIH finishing clinical genetics

NOTE Confidence: 0.782711955

00:06:18.866 --> 00:06:21.878 and clinical biochemical genetics.

NOTE Confidence: 0.782711955

00:06:21.880 --> 00:06:25.192 His was funding ACMG American College

NOTE Confidence: 0.782711955

00:06:25.192 --> 00:06:28.020 of medical genetics fellow he was

NOTE Confidence: 0.782711955

00:06:28.020 --> 00:06:29.880 just what dinner tonight last night

NOTE Confidence: 0.782711955

00:06:29.880 --> 00:06:32.184 he was telling a story at that

NOTE Confidence: 0.782711955

00:06:32.184 --> 00:06:34.176 time doing board exam for medical

NOTE Confidence: 0.782711955

00:06:34.176 --> 00:06:35.906 genetics like half people write

NOTE Confidence: 0.782711955

00:06:35.906 --> 00:06:37.916 an exam for other half trainees.

NOTE Confidence: 0.782711955

00:06:37.920 --> 00:06:40.519 So that's what how how the history goes.

NOTE Confidence: 0.782711955

00:06:40.519 --> 00:06:42.997 So maybe it's easy then today,

NOTE Confidence: 0.782711955

00:06:43.000 --> 00:06:44.953 so you don't have to go to

NOTE Confidence: 0.782711955

00:06:44.953 --> 00:06:46.440 database to pick that one.

NOTE Confidence: 0.782711955

00:06:46.440 --> 00:06:48.740 He's researched clearly he's

NOTE Confidence: 0.782711955

00:06:48.740 --> 00:06:51.240 a physician scientist and it's

NOTE Confidence: 0.782711955

00:06:51.240 --> 00:06:53.560 a role model for me for sure.

NOTE Confidence: 0.782711955

00:06:53.560 --> 00:06:56.014 And he covered dedicated time to

NOTE Confidence: 0.782711955

00:06:56.014 --> 00:06:58.860 discover the gene for rare disease

NOTE Confidence: 0.782711955

00:06:58.860 --> 00:07:01.675 primarily by chemical genetic disorder.

NOTE Confidence: 0.782711955

00:07:01.680 --> 00:07:04.875 Now he went ahead and did a lot of

NOTE Confidence: 0.782711955

00:07:04.880 --> 00:07:06.852 basic science study understanding

NOTE Confidence: 0.782711955

00:07:06.852 --> 00:07:09.810 what's the mechanism for that disease

NOTE Confidence: 0.782711955

00:07:09.882 --> 00:07:12.160 then continue for developer treatment,

NOTE Confidence: 0.782711955

00:07:12.160 --> 00:07:13.160 engage FDA.

NOTE Confidence: 0.782711955

00:07:13.160 --> 00:07:15.035 He developed a multiple treatment

NOTE Confidence: 0.782711955

00:07:15.035 --> 00:07:17.028 for rare disease and a lot of

NOTE Confidence: 0.782711955

00:07:17.028 --> 00:07:17.679 the signature program.

NOTE Confidence: 0.782711955

00:07:17.680 --> 00:07:19.903 If I look at the CV that's a list

NOTE Confidence: 0.782711955

00:07:19.903 --> 00:07:22.155 of engagement with FDA and make

NOTE Confidence: 0.782711955

00:07:22.155 --> 00:07:24.865 sure the patient in the clinical

NOTE Confidence: 0.782711955

00:07:24.865 --> 00:07:27.955 gather that hope to after diagnosis.

NOTE Confidence: 0.782711955

00:07:27.960 --> 00:07:31.980 And this clearly is a proliferix kind of Pi.

NOTE Confidence: 0.782711955

00:07:31.980 --> 00:07:36.781 He published 650 paper and a lot

NOTE Confidence: 0.782711955

00:07:36.781 --> 00:07:39.350 of clinical protocol and a lot of

NOTE Confidence: 0.782711955

00:07:39.438 --> 00:07:42.457 product treatment FDA approval there.

NOTE Confidence: 0.782711955

00:07:42.457 --> 00:07:45.199 Then he also discovered the signature

NOTE Confidence: 0.782711955

00:07:45.199 --> 00:07:48.310 program is he discovered the molecular

NOTE Confidence: 0.782711955

00:07:48.310 --> 00:07:51.090 basis for the cystinosis or sciatic

NOTE Confidence: 0.782711955

00:07:51.090 --> 00:07:53.085 acid disorder which is pretty rare for

NOTE Confidence: 0.782711955

00:07:53.085 --> 00:07:55.080 many of you probably have not heard

NOTE Confidence: 0.782711955

00:07:55.080 --> 00:07:56.978 about and he probably will tell the

NOTE Confidence: 0.782711955

00:07:56.978 --> 00:07:58.714 story too and the many other rare

NOTE Confidence: 0.782711955

00:07:58.720 --> 00:08:01.720 disease most in the metabolic related.

NOTE Confidence: 0.782711955

00:08:01.720 --> 00:08:05.860 Then his group after study UDP

NOTE Confidence: 0.782711955

00:08:05.860 --> 00:08:10.115 discovered almost 300 disease gene and

NOTE Confidence: 0.782711955

00:08:10.115 --> 00:08:14.588 the disorder and the more then as a

NOTE Confidence: 0.782711955

00:08:14.588 --> 00:08:18.884 mentor I should mention Bill Trader

NOTE Confidence: 0.782711955

00:08:18.884 --> 00:08:22.832 train 42 clinical biochemical genetic

NOTE Confidence: 0.782711955

00:08:22.832 --> 00:08:26.934 fellow almost ten 110th of anti people

NOTE Confidence: 0.782711955

00:08:26.934 --> 00:08:30.280 board certified in my specialty.

NOTE Confidence: 0.782711955

00:08:30.280 --> 00:08:32.660 He was the first one push for

NOTE Confidence: 0.782711955

00:08:32.660 --> 00:08:35.056 the new specialty called medical

NOTE Confidence: 0.782711955

00:08:35.056 --> 00:08:36.358 biochemical genetics,

NOTE Confidence: 0.782711955

00:08:36.360 --> 00:08:38.960 which I was the beneficiary.

NOTE Confidence: 0.782711955

00:08:38.960 --> 00:08:43.800 I was the first founding fellow 2009 five

NOTE Confidence: 0.782711955

00:08:43.800 --> 00:08:47.720 for because he's a vision for that program.

NOTE Confidence: 0.782711955

00:08:47.720 --> 00:08:50.736 So you can see many of people he

NOTE Confidence: 0.782711955

00:08:50.736 --> 00:08:52.699 trained including here and many

NOTE Confidence: 0.782711955

00:08:52.699 --> 00:08:54.961 other institution is a leader in

NOTE Confidence: 0.782711955

00:08:54.961 --> 00:08:57.000 the biochemical genetics.

NOTE Confidence: 0.782711955

00:08:57.000 --> 00:08:57.720 As I said,

NOTE Confidence: 0.782711955

00:08:57.720 --> 00:09:00.440 I would leave the UDPUT not touch that part.

NOTE Confidence: 0.782711955

00:09:00.440 --> 00:09:02.240 He would tell the story.

NOTE Confidence: 0.782711955

00:09:02.240 --> 00:09:05.782 Because of that you can clearly see

NOTE Confidence: 0.782711955

00:09:05.782 --> 00:09:08.160 how much accomplishment and reward

NOTE Confidence: 0.782711955

00:09:08.160 --> 00:09:10.308 that he has got. It's a long list.

NOTE Confidence: 0.782711955

00:09:10.308 --> 00:09:11.793 I just pick a few.

NOTE Confidence: 0.782711955

00:09:11.800 --> 00:09:14.320 I I I actually copy from his CV

NOTE Confidence: 0.782711955

00:09:14.320 --> 00:09:16.796 make sure I cover some major one.

NOTE Confidence: 0.782711955

00:09:16.800 --> 00:09:19.015 He received multiple time for

NOTE Confidence: 0.782711955

00:09:19.015 --> 00:09:21.230 NIH director award many years

NOTE Confidence: 0.782711955

00:09:21.307 --> 00:09:22.960 throughout his career.

NOTE Confidence: 0.782711955

00:09:22.960 --> 00:09:23.451 He,

NOTE Confidence: 0.782711955

00:09:23.451 --> 00:09:27.870 as NICHD Hall of the honor only 15 scientists

NOTE Confidence: 0.682643064166667

00:09:27.975 --> 00:09:30.280 was recognized, would recognize

NOTE Confidence: 0.731188824285714

00:09:32.320 --> 00:09:35.757 2013, including three or four Nobel Laureate.

NOTE Confidence: 0.731188824285714

00:09:35.760 --> 00:09:38.848 In that list he was the president of

NOTE Confidence: 0.731188824285714

00:09:38.848 --> 00:09:41.718 a Society of Embroiler metabolism.

NOTE Confidence: 0.731188824285714

00:09:41.720 --> 00:09:44.240 He received the Nathan Davis Award,

NOTE Confidence: 0.731188824285714

00:09:44.240 --> 00:09:46.352 outstanding government service

NOTE Confidence: 0.731188824285714

00:09:46.352 --> 00:09:49.800 from AMA Euris Lifetime Chiefman

NOTE Confidence: 0.731188824285714

00:09:49.800 --> 00:09:54.135 Award and 2019 he was elected for

NOTE Confidence: 0.731188824285714

00:09:54.135 --> 00:09:56.515 National Academy for Medicine.

NOTE Confidence: 0.731188824285714

00:09:56.520 --> 00:09:58.614 With that I guess I should

NOTE Confidence: 0.731188824285714

00:09:58.614 --> 00:10:00.560 say a few personal notes.

NOTE Confidence: 0.731188824285714

00:10:00.560 --> 00:10:02.751 As you know I I'm clinical genetics

NOTE Confidence: 0.731188824285714

00:10:02.751 --> 00:10:05.402 also clinical I think I call them

NOTE Confidence: 0.731188824285714

00:10:05.402 --> 00:10:06.638 medical biochemical genetics,

NOTE Confidence: 0.731188824285714

00:10:06.640 --> 00:10:08.064 not clinical biochemical genetics

NOTE Confidence: 0.731188824285714

00:10:08.064 --> 00:10:10.200 that's more lab to direct it.

NOTE Confidence: 0.731188824285714

00:10:10.200 --> 00:10:13.152 So I definitely know Bill's all works before

NOTE Confidence: 0.731188824285714

00:10:13.152 --> 00:10:16.360 I know him in person so we can know him.

NOTE Confidence: 0.731188824285714

00:10:16.360 --> 00:10:20.308 It's when the UDN when I was at Duke.

NOTE Confidence: 0.731188824285714

00:10:20.308 --> 00:10:23.736 We are part of a clinical side of the UDN

NOTE Confidence: 0.731188824285714

00:10:23.736 --> 00:10:26.380 funding like the first seven side name.

NOTE Confidence: 0.731188824285714

00:10:26.380 --> 00:10:29.040 So we met her before the COVID.

NOTE Confidence: 0.731188824285714

00:10:29.040 --> 00:10:31.385 We met her regularly quarterly

NOTE Confidence: 0.731188824285714

00:10:31.385 --> 00:10:34.960 at DC or some other House Hotel.

NOTE Confidence: 0.731188824285714

00:10:34.960 --> 00:10:38.320 Now we're starting to engage with a

NOTE Confidence: 0.731188824285714

00:10:38.320 --> 00:10:41.820 Bill and learn he's a he's a great

NOTE Confidence: 0.731188824285714

00:10:41.820 --> 00:10:43.880 visionary leader for this field.

NOTE Confidence: 0.731188824285714

00:10:43.880 --> 00:10:45.343 One thing I like very much is

NOTE Confidence: 0.731188824285714

00:10:45.343 --> 00:10:46.879 every time you notice Consortium,

NOTE Confidence: 0.731188824285714

00:10:46.880 --> 00:10:48.784 so many people in a meeting and he

NOTE Confidence: 0.731188824285714

00:10:48.784 --> 00:10:50.746 often time opened up the talk at

NOTE Confidence: 0.731188824285714

00:10:50.746 --> 00:10:52.176 the beginning for the Consortium

NOTE Confidence: 0.731188824285714

00:10:52.229 --> 00:10:54.182 as you know to try to get all these

NOTE Confidence: 0.731188824285714

00:10:54.182 --> 00:10:56.496 smart people in the same room to

NOTE Confidence: 0.731188824285714

00:10:56.496 --> 00:10:57.840 talking some challenging topics,

NOTE Confidence: 0.731188824285714

00:10:57.840 --> 00:10:58.640 a very,

NOTE Confidence: 0.731188824285714

00:10:58.640 --> 00:11:00.240 very sometimes very challenging.

NOTE Confidence: 0.731188824285714

00:11:00.240 --> 00:11:01.560 So Pierre usually opened up

NOTE Confidence: 0.670606933333333

00:11:03.600 --> 00:11:06.198 sometimes kind of light moment joke

NOTE Confidence: 0.670606933333333

00:11:06.200 --> 00:11:08.404 1st and make everyone laugh first.

NOTE Confidence: 0.670606933333333

00:11:08.404 --> 00:11:11.238 So as you can see it when you laugh,

NOTE Confidence: 0.670606933333333

00:11:11.240 --> 00:11:13.480 everything can synchronize very well.

NOTE Confidence: 0.670606933333333

00:11:13.480 --> 00:11:15.400 After that initial sort of first

NOTE Confidence: 0.670606933333333

00:11:15.400 --> 00:11:17.297 few minutes you always can find

NOTE Confidence: 0.670606933333333

00:11:17.297 --> 00:11:18.953 a way to make everyone laugh.

NOTE Confidence: 0.670606933333333

00:11:18.960 --> 00:11:20.580 And before we get in serious

NOTE Confidence: 0.670606933333333

00:11:20.580 --> 00:11:23.270 about our serious topic so that

NOTE Confidence: 0.670606933333333

00:11:23.270 --> 00:11:24.920 I was fair bit impressed,

NOTE Confidence: 0.670606933333333

00:11:24.920 --> 00:11:26.677 I'm missing out a lot of things

NOTE Confidence: 0.670606933333333

00:11:26.680 --> 00:11:28.320 are really good to hear.

NOTE Confidence: 0.670606933333333

00:11:28.320 --> 00:11:30.864 I hope we can join you back and

NOTE Confidence: 0.670606933333333

00:11:30.864 --> 00:11:33.163 enjoy that part of learn how you

NOTE Confidence: 0.670606933333333

00:11:33.163 --> 00:11:36.440 are leading this consortium and and

NOTE Confidence: 0.670606933333333

00:11:36.440 --> 00:11:38.080 visionary leader for this very,

NOTE Confidence: 0.670606933333333

00:11:38.080 --> 00:11:40.176 very challenging topic for

NOTE Confidence: 0.670606933333333

00:11:40.176 --> 00:11:42.796 often time in the medicine.

NOTE Confidence: 0.670606933333333

00:11:42.800 --> 00:11:47.048 And also I think 2015 was a Project

NOTE Confidence: 0.670606933333333

00:11:47.048 --> 00:11:50.442 B and I have made a trip to the

NOTE Confidence: 0.670606933333333

00:11:50.442 --> 00:11:53.940 Shanghai to kind of disseminate all

NOTE Confidence: 0.670606933333333

00:11:53.940 --> 00:11:57.537 Nash international outreach for UDA P

NOTE Confidence: 0.670606933333333

00:11:57.537 --> 00:12:00.766 program that was great fun to when together.

NOTE Confidence: 0.670606933333333

00:12:00.766 --> 00:12:03.190 I really still remembers a lot of people

NOTE Confidence: 0.670606933333333

00:12:03.254 --> 00:12:05.518 also almost try to show one picture here.

NOTE Confidence: 0.670606933333333

00:12:05.520 --> 00:12:06.880 We will definitely show

NOTE Confidence: 0.670606933333333

00:12:06.880 --> 00:12:08.434 next time with that Bill,

NOTE Confidence: 0.670606933333333

00:12:08.434 --> 00:12:09.598 thank you so much for coming

NOTE Confidence: 0.670606933333333

00:12:09.598 --> 00:12:10.931 from your busy schedule and we're

NOTE Confidence: 0.670606933333333

00:12:10.931 --> 00:12:12.116 looking forward to your talk.

NOTE Confidence: 0.896220784117647

00:12:16.680 --> 00:12:17.640 Thanks very much.

NOTE Confidence: 0.896220784117647

00:12:17.640 --> 00:12:19.880 I'll try to get people to laugh

NOTE Confidence: 0.896220784117647

00:12:19.948 --> 00:12:22.034 with me rather than laugh at me.

NOTE Confidence: 0.896220784117647

00:12:22.040 --> 00:12:25.080 And also some of the jokes that I tell here,

NOTE Confidence: 0.896220784117647

00:12:25.080 --> 00:12:27.558 I can't actually tell in Shanghai,

NOTE Confidence: 0.896220784117647

00:12:27.560 --> 00:12:30.276 but where's this all? Here we go.

NOTE Confidence: 0.896220784117647

00:12:30.280 --> 00:12:32.520 So and I want to tell stories today,

NOTE Confidence: 0.896220784117647

00:12:32.520 --> 00:12:35.928 stories about unusual diseases and mechanisms

NOTE Confidence: 0.896220784117647

00:12:35.928 --> 00:12:40.040 of disease that you're not so likely to see,

NOTE Confidence: 0.896220784117647

00:12:40.040 --> 00:12:42.984 but that still interest us and may have

NOTE Confidence: 0.896220784117647

00:12:42.984 --> 00:12:45.136 applications to common disease because

NOTE Confidence: 0.896220784117647

00:12:45.136 --> 00:12:48.272 that's what happens with some rare diseases.

NOTE Confidence: 0.896220784117647

00:12:48.280 --> 00:12:51.140 And I want to mention that Cindy Tift is the

NOTE Confidence: 0.896220784117647

00:12:51.213 --> 00:12:53.719 Director of the pediatric portion of the

NOTE Confidence: 0.896220784117647

00:12:53.719 --> 00:12:56.036 UDP and David Adams does the bioinformatics.

NOTE Confidence: 0.896220784117647

00:12:56.040 --> 00:12:57.750 And we have two great neurologists

NOTE Confidence: 0.896220784117647

00:12:57.750 --> 00:12:59.611 I mentioned here and two great

NOTE Confidence: 0.896220784117647

00:12:59.611 --> 00:13:01.276 internists and a psych coordinator.

NOTE Confidence: 0.896220784117647

00:13:01.280 --> 00:13:04.997 And this program is supported by the

NOTE Confidence: 0.896220784117647

00:13:05.000 --> 00:13:07.373 volunteer efforts of a huge number of

NOTE Confidence: 0.896220784117647

00:13:07.373 --> 00:13:09.467 experts within the intro program of

NOTE Confidence: 0.896220784117647

00:13:09.467 --> 00:13:11.840 the NIH experts in rare diseases there.

NOTE Confidence: 0.896220784117647

00:13:11.840 --> 00:13:14.600 This program was established in and

NOTE Confidence: 0.896220784117647

00:13:14.600 --> 00:13:17.652 announced in May of 2008 with two goals.

NOTE Confidence: 0.896220784117647

00:13:17.652 --> 00:13:20.012 One to help people reach a diagnosis

NOTE Confidence: 0.896220784117647

00:13:20.012 --> 00:13:21.932 when they've sought A diagnosis

NOTE Confidence: 0.896220784117647

00:13:21.932 --> 00:13:24.200 and haven't been able to get one,

NOTE Confidence: 0.896220784117647

00:13:24.200 --> 00:13:26.216 and the other is to discover new

NOTE Confidence: 0.896220784117647

00:13:26.216 --> 00:13:27.750 things about biochemistry and cell

NOTE Confidence: 0.896220784117647

00:13:27.750 --> 00:13:29.280 biology and mechanisms of disease.

NOTE Confidence: 0.896220784117647

00:13:29.280 --> 00:13:31.160 So to contribute to medicine.

NOTE Confidence: 0.896220784117647

00:13:31.160 --> 00:13:33.528 And the way it works is that the

NOTE Confidence: 0.896220784117647

00:13:33.528 --> 00:13:35.130 applicants submit their medical records

NOTE Confidence: 0.896220784117647

00:13:35.130 --> 00:13:38.009 and I for the adults and doctor TIFF for

NOTE Confidence: 0.896220784117647

00:13:38.009 --> 00:13:40.165 the children will look them over and

NOTE Confidence: 0.896220784117647

00:13:40.165 --> 00:13:43.438 triage them to different experts to say,

NOTE Confidence: 0.896220784117647

00:13:43.440 --> 00:13:45.558 offer an opinion about whether this

NOTE Confidence: 0.896220784117647

00:13:45.558 --> 00:13:47.472 is reasonable or not as something

NOTE Confidence: 0.896220784117647

00:13:47.472 --> 00:13:48.720 that we should study.

NOTE Confidence: 0.896220784117647

00:13:48.720 --> 00:13:52.176 We only accept about 1/3 or so of the

NOTE Confidence: 0.896220784117647

00:13:52.176 --> 00:13:54.630 people who apply and we offer some advice

NOTE Confidence: 0.896220784117647

00:13:54.630 --> 00:13:56.758 to the others and the ones that we see,

NOTE Confidence: 0.896220784117647

00:13:56.760 --> 00:13:59.560 we see for a week at the NIH free of charge.

NOTE Confidence: 0.896220784117647

00:13:59.560 --> 00:14:02.600 So we don't charge any third parties either.

NOTE Confidence: 0.896220784117647

00:14:02.600 --> 00:14:04.840 Over the course of the last 15 or 16 years,

NOTE Confidence: 0.896220784117647

00:14:04.840 --> 00:14:07.318 we've seen over 6000 medical records

NOTE Confidence: 0.896220784117647

00:14:07.318 --> 00:14:09.580 and seen over 1600 at the NIH.

NOTE Confidence: 0.896220784117647

00:14:09.580 --> 00:14:12.314 A lot of kids and more than half of

NOTE Confidence: 0.896220784117647

00:14:12.314 --> 00:14:14.199 our cases are neurological cases,

NOTE Confidence: 0.896220784117647

00:14:14.200 --> 00:14:17.440 a lot of exomes and especially family exomes.

NOTE Confidence: 0.896220784117647

00:14:17.440 --> 00:14:19.876 We get a skin biopsy for fibroblast

NOTE Confidence: 0.896220784117647

00:14:19.876 --> 00:14:22.235 culture to do some gene function

NOTE Confidence: 0.896220784117647

00:14:22.235 --> 00:14:24.704 studies on about 70% of the patients.

NOTE Confidence: 0.896220784117647

00:14:24.704 --> 00:14:27.570 We see a lot of diagnosis and

NOTE Confidence: 0.896220784117647

00:14:27.570 --> 00:14:28.920 publications as well.

NOTE Confidence: 0.896220784117647

00:14:28.920 --> 00:14:31.840 And for the genetics,

NOTE Confidence: 0.896220784117647

00:14:31.840 --> 00:14:34.760 we can do customized

NOTE Confidence: 0.896220784117647

00:14:34.760 --> 00:14:35.924 personalized phenotyping,

NOTE Confidence: 0.896220784117647

00:14:35.924 --> 00:14:39.217 but also some of the genetics

NOTE Confidence: 0.896220784117647

00:14:39.217 --> 00:14:40.348 that's available commercially.

NOTE Confidence: 0.896220784117647

00:14:40.348 --> 00:14:43.572 We also do snip arrays on many of our

NOTE Confidence: 0.896220784117647

00:14:43.572 --> 00:14:45.077 patients and excellence and genomes

NOTE Confidence: 0.896220784117647

00:14:45.077 --> 00:14:47.549 as I mentioned and for some of them

NOTE Confidence: 0.896220784117647

00:14:47.549 --> 00:14:49.234 when we have multiple different

NOTE Confidence: 0.896220784117647

00:14:49.234 --> 00:14:52.078 candidate genes and variants and genes,

NOTE Confidence: 0.896220784117647

00:14:52.080 --> 00:14:54.050 we'll do functional studies in

NOTE Confidence: 0.896220784117647

00:14:54.050 --> 00:14:56.422 fibroblasts and there's a model organisms

NOTE Confidence: 0.896220784117647

00:14:56.422 --> 00:14:58.760 core as well that we can employ.

NOTE Confidence: 0.896220784117647

00:14:58.760 --> 00:15:01.070 I wanted to give you some examples

NOTE Confidence: 0.896220784117647

00:15:01.070 --> 00:15:03.427 of discovery and this is an early

NOTE Confidence: 0.896220784117647

00:15:03.427 --> 00:15:04.399 discovery of ours.

NOTE Confidence: 0.896220784117647

00:15:04.400 --> 00:15:07.748 We saw five adults from the Kentucky,

NOTE Confidence: 0.896220784117647

00:15:07.748 --> 00:15:11.145 Ohio region who are all siblings and

NOTE Confidence: 0.896220784117647

00:15:11.145 --> 00:15:13.215 they had claudication in their lower

NOTE Confidence: 0.896220784117647

00:15:13.215 --> 00:15:15.080 extremities because of ischemic pain.

NOTE Confidence: 0.896220784117647

00:15:15.080 --> 00:15:17.719 So vascular insufficiency is what they had.

NOTE Confidence: 0.896220784117647

00:15:17.720 --> 00:15:20.600 Their coronaries were largely

NOTE Confidence: 0.679609168

00:15:20.600 --> 00:15:24.670 spirit, but these are their arteries

NOTE Confidence: 0.679609168

00:15:24.670 --> 00:15:27.680 and this is there's no contrast here.

NOTE Confidence: 0.679609168

00:15:27.680 --> 00:15:29.878 So this is all calcification of their

NOTE Confidence: 0.679609168

00:15:29.878 --> 00:15:31.360 femoral and popliteal arteries.

NOTE Confidence: 0.679609168

00:15:31.360 --> 00:15:32.236 And here it is on PA.

NOTE Confidence: 0.396687728333333

00:15:34.280 --> 00:15:37.652 And see the Der Salus petis calcified here.

NOTE Confidence: 0.396687728333333

00:15:37.652 --> 00:15:41.800 No wonder they had pain and they were

NOTE Confidence: 0.396687728333333

00:15:41.800 --> 00:15:43.920 surviving off their collaterals.

NOTE Confidence: 0.396687728333333

00:15:43.920 --> 00:15:46.188 And they also had in the metacarpal

NOTE Confidence: 0.396687728333333

00:15:46.188 --> 00:15:48.000 phalangeal joints some calcification.

NOTE Confidence: 0.396687728333333

00:15:48.000 --> 00:15:50.800 There you can see that as well.

NOTE Confidence: 0.396687728333333

00:15:50.800 --> 00:15:53.080 Well, it turns out that their

NOTE Confidence: 0.396687728333333

00:15:53.080 --> 00:15:54.600 parents were third cousins,

NOTE Confidence: 0.396687728333333

00:15:54.600 --> 00:15:56.382 and we know that the first

NOTE Confidence: 0.396687728333333

00:15:56.382 --> 00:15:58.400 cousins share 1/8 of their genes.

NOTE Confidence: 0.396687728333333

00:15:58.400 --> 00:16:00.759 Second cousins share 132nd of their genes.

NOTE Confidence: 0.396687728333333

00:16:00.760 --> 00:16:03.640 Third cousins share one 128th of their genes.

NOTE Confidence: 0.396687728333333

00:16:03.640 --> 00:16:07.264 So if we're going to consider this a

NOTE Confidence: 0.396687728333333

00:16:07.264 --> 00:16:09.630 recessive disorder that may be caused

NOTE Confidence: 0.396687728333333

00:16:09.630 --> 00:16:12.240 by the consanguinity that they have,

NOTE Confidence: 0.396687728333333

00:16:12.240 --> 00:16:15.840 we can look in one 128th of their genes,

NOTE Confidence: 0.396687728333333

00:16:15.840 --> 00:16:17.040 that is to say,

NOTE Confidence: 0.396687728333333

00:16:17.040 --> 00:16:19.518 the regions in which they are homozygous.

NOTE Confidence: 0.396687728333333

00:16:19.520 --> 00:16:21.445 And the reason that that's important is

NOTE Confidence: 0.396687728333333

00:16:21.445 --> 00:16:23.479 because in that region of homozygosity,

NOTE Confidence: 0.396687728333333

00:16:23.480 --> 00:16:24.920 if you have one variant,

NOTE Confidence: 0.396687728333333

00:16:24.920 --> 00:16:26.480 you're going to have two variants,

NOTE Confidence: 0.396687728333333

00:16:26.480 --> 00:16:27.845 and this could have caused

NOTE Confidence: 0.396687728333333

00:16:27.845 --> 00:16:28.878 a recessive disease.

NOTE Confidence: 0.396687728333333

00:16:28.878 --> 00:16:31.152 Well, it turns out that there

NOTE Confidence: 0.396687728333333

00:16:31.152 --> 00:16:33.477 were such regions on a SNP array,

NOTE Confidence: 0.396687728333333

00:16:33.480 --> 00:16:35.016 single nucleotide polymorphisms.

NOTE Confidence: 0.396687728333333

00:16:35.016 --> 00:16:38.600 That disarray contains a million of those,

NOTE Confidence: 0.396687728333333

00:16:38.600 --> 00:16:41.554 meaning that since they're 3.2 billion bases,

NOTE Confidence: 0.396687728333333

00:16:41.560 --> 00:16:46.636 these SNPs are about 3000 bases apart.

NOTE Confidence: 0.396687728333333

00:16:46.640 --> 00:16:48.536 And every one of these little

NOTE Confidence: 0.396687728333333

00:16:48.536 --> 00:16:50.160 blue dots is a SNP.

NOTE Confidence: 0.396687728333333

00:16:50.160 --> 00:16:54.558 And so the those blue dots,

NOTE Confidence: 0.396687728333333

00:16:54.560 --> 00:16:56.000 the separation between them

NOTE Confidence: 0.396687728333333

00:16:56.000 --> 00:16:57.560 represents 3000 bases.

NOTE Confidence: 0.396687728333333

00:16:57.560 --> 00:17:00.440 So this is a region of chromosome 6,

NOTE Confidence: 0.396687728333333

00:17:00.440 --> 00:17:02.560 and what's shown those dots

NOTE Confidence: 0.396687728333333

00:17:02.560 --> 00:17:04.680 are only the heterozygous SNPs.

NOTE Confidence: 0.396687728333333

00:17:04.680 --> 00:17:06.600 So we've eliminated the top ones

NOTE Confidence: 0.396687728333333

00:17:06.600 --> 00:17:08.872 which are the AAS and the bottom

NOTE Confidence: 0.396687728333333

00:17:08.872 --> 00:17:11.016 ones which are the BBS and this,

NOTE Confidence: 0.396687728333333

00:17:11.016 --> 00:17:12.752 these are the ABS that you see.

NOTE Confidence: 0.396687728333333

00:17:12.760 --> 00:17:16.360 And you can see that for the siblings here,

NOTE Confidence: 0.396687728333333

00:17:16.360 --> 00:17:18.342 that's children 12345.

NOTE Confidence: 0.396687728333333

00:17:18.342 --> 00:17:20.634 They all have a region with

NOTE Confidence: 0.396687728333333

00:17:20.634 --> 00:17:21.398 no heterozygosity.

NOTE Confidence: 0.396687728333333

00:17:21.400 --> 00:17:23.356 So they're homozygous in this region,

NOTE Confidence: 0.396687728333333

00:17:23.360 --> 00:17:25.640 meaning that this if there's a variant here,

NOTE Confidence: 0.396687728333333

00:17:25.640 --> 00:17:27.440 they're going to have it on

NOTE Confidence: 0.396687728333333

00:17:27.440 --> 00:17:28.640 both of their alleles.

NOTE Confidence: 0.396687728333333

00:17:28.640 --> 00:17:30.705 And that was a region of 22

NOTE Confidence: 0.396687728333333

00:17:30.705 --> 00:17:32.280 mega bases with 92 genes.

NOTE Confidence: 0.396687728333333

00:17:32.280 --> 00:17:33.477 And our heart,

NOTE Confidence: 0.396687728333333

00:17:33.477 --> 00:17:35.871 lung and blood associates picked out

NOTE Confidence: 0.396687728333333

00:17:35.871 --> 00:17:38.493 anti 5E as a candidate for causing

NOTE Confidence: 0.396687728333333

00:17:38.493 --> 00:17:42.776 this disease and that encodes CD 73,

NOTE Confidence: 0.396687728333333

00:17:42.776 --> 00:17:45.824 an enzyme in the vascular endothelium

NOTE Confidence: 0.396687728333333

00:17:45.824 --> 00:17:48.722 that converts AMP to adenosine

NOTE Confidence: 0.396687728333333

00:17:48.722 --> 00:17:50.516 and inorganic phosphate.

NOTE Confidence: 0.396687728333333

00:17:50.520 --> 00:17:53.544 And in fact these five individuals

NOTE Confidence: 0.396687728333333

00:17:53.544 --> 00:17:58.077 you see here had all homozygous

NOTE Confidence: 0.396687728333333

00:17:58.077 --> 00:18:00.939 nonsense mutation shown here we found

NOTE Confidence: 0.396687728333333

00:18:00.939 --> 00:18:03.503 another family with three affected

NOTE Confidence: 0.396687728333333

00:18:03.503 --> 00:18:06.158 individuals with a different mutation,

NOTE Confidence: 0.396687728333333

00:18:06.160 --> 00:18:09.004 also homozygous and then a compound

NOTE Confidence: 0.396687728333333

00:18:09.004 --> 00:18:10.872 heterozygous family as well.

NOTE Confidence: 0.396687728333333

00:18:10.872 --> 00:18:13.192 So those individuals in three

NOTE Confidence: 0.396687728333333

00:18:13.192 --> 00:18:14.120 different families.

NOTE Confidence: 0.396687728333333

00:18:14.120 --> 00:18:15.776 And it turns out that the

NOTE Confidence: 0.396687728333333

00:18:15.776 --> 00:18:16.880 fibroblasts expressed this gene.

NOTE Confidence: 0.396687728333333

00:18:16.880 --> 00:18:19.680 So here's NT 5E expression in normals.

NOTE Confidence: 0.396687728333333

00:18:19.680 --> 00:18:22.520 And then in two of the affected individuals,

NOTE Confidence: 0.396687728333333

00:18:22.520 --> 00:18:24.385 the enzyme activity was also

NOTE Confidence: 0.396687728333333

00:18:24.385 --> 00:18:25.877 decreased in the fibroblast,

NOTE Confidence: 0.396687728333333

00:18:25.880 --> 00:18:28.075 and this enzyme activity could

NOTE Confidence: 0.396687728333333

00:18:28.075 --> 00:18:30.270 be rescued by transduction with

NOTE Confidence: 0.396687728333333

00:18:30.345 --> 00:18:32.397 a vector that contains CD 73,

NOTE Confidence: 0.396687728333333

00:18:32.400 --> 00:18:33.408 the missing enzyme.

NOTE Confidence: 0.396687728333333

00:18:33.408 --> 00:18:35.760 So we're trying to prove fusality here,

NOTE Confidence: 0.396687728333333

00:18:35.760 --> 00:18:37.920 and that's pretty much how we get it.

NOTE Confidence: 0.396687728333333

00:18:37.920 --> 00:18:38.417 Furthermore,

NOTE Confidence: 0.396687728333333

00:18:38.417 --> 00:18:41.399 the fibroblasts express not only the

NOTE Confidence: 0.396687728333333

00:18:41.399 --> 00:18:44.831 genotype but a phenotype and the

NOTE Confidence: 0.396687728333333

00:18:44.831 --> 00:18:47.315 phenotype was increased alkaline

NOTE Confidence: 0.396687728333333

00:18:47.315 --> 00:18:48.557 phosphatase activity.

NOTE Confidence: 0.396687728333333

00:18:48.560 --> 00:18:50.000 You'll see why this is important,

NOTE Confidence: 0.396687728333333

00:18:50.000 --> 00:18:54.090 but this is the affected patients

NOTE Confidence: 0.396687728333333

00:18:54.090 --> 00:18:56.210 cultures of fibroblast stained

NOTE Confidence: 0.396687728333333

00:18:56.210 --> 00:18:57.800 for alkaline phosphatase.

NOTE Confidence: 0.396687728333333

00:18:57.800 --> 00:18:59.936 This is the control and when

NOTE Confidence: 0.396687728333333

00:18:59.936 --> 00:19:01.360 you treat with adenosine,

NOTE Confidence: 0.966290021428571

00:19:01.360 --> 00:19:06.040 which is the missing product of the CD 73,

NOTE Confidence: 0.966290021428571

00:19:06.040 --> 00:19:09.240 you mitigate the alkaline phosphatase

NOTE Confidence: 0.966290021428571

00:19:09.240 --> 00:19:11.925 excess and in other words, it rescues it.

NOTE Confidence: 0.966290021428571

00:19:11.925 --> 00:19:13.600 It not only rescues that,

NOTE Confidence: 0.966290021428571

00:19:13.600 --> 00:19:16.960 but it rescues calcification.

NOTE Confidence: 0.966290021428571

00:19:16.960 --> 00:19:20.353 Alizarin red staining is a

NOTE Confidence: 0.966290021428571

00:19:20.353 --> 00:19:22.637 reflection of calcium accumulation.

NOTE Confidence: 0.966290021428571

00:19:22.640 --> 00:19:23.960 So here's the affected

NOTE Confidence: 0.966290021428571

00:19:23.960 --> 00:19:25.280 compared to the normal.

NOTE Confidence: 0.966290021428571

00:19:25.280 --> 00:19:30.260 And here is the cell culture of the

NOTE Confidence: 0.966290021428571

00:19:30.260 --> 00:19:31.775 affected individuals transduced

NOTE Confidence: 0.966290021428571

00:19:31.775 --> 00:19:34.312 with a lentivirus containing CD73.

NOTE Confidence: 0.966290021428571

00:19:34.312 --> 00:19:37.360 You see it corrects the calcification.

NOTE Confidence: 0.966290021428571

00:19:37.360 --> 00:19:38.563 So does adenosine,

NOTE Confidence: 0.966290021428571

00:19:38.563 --> 00:19:40.167 again the product that's

NOTE Confidence: 0.966290021428571

00:19:40.167 --> 00:19:42.480 missing and so does levamisol,

NOTE Confidence: 0.966290021428571

00:19:42.480 --> 00:19:44.168 which is an inhibitor

NOTE Confidence: 0.966290021428571

00:19:44.168 --> 00:19:45.434 of alkaline phosphatase.

NOTE Confidence: 0.966290021428571

00:19:45.440 --> 00:19:48.440 So alkaline phosphatase is very important,

NOTE Confidence: 0.966290021428571

00:19:48.440 --> 00:19:50.638 has a very important role in this.

NOTE Confidence: 0.966290021428571

00:19:50.640 --> 00:19:52.957 And that that role is shown here.

NOTE Confidence: 0.966290021428571

00:19:52.960 --> 00:19:55.845 Ordinarily on the vascular endothelium

NOTE Confidence: 0.966290021428571

00:19:55.845 --> 00:19:59.630 you have CD 73 converting AMP to

NOTE Confidence: 0.966290021428571

00:19:59.630 --> 00:20:02.184 adenosine and then adenosine interacts

NOTE Confidence: 0.966290021428571

00:20:02.184 --> 00:20:04.714 with the vascular cell receptors.

NOTE Confidence: 0.966290021428571

00:20:04.720 --> 00:20:07.845 To trophically inhibit tissue non

NOTE Confidence: 0.966290021428571

00:20:07.845 --> 00:20:09.720 specific alkaline phosphatase.

NOTE Confidence: 0.966290021428571

00:20:09.720 --> 00:20:12.044 When that doesn't happen and and you

NOTE Confidence: 0.966290021428571

00:20:12.044 --> 00:20:14.198 see that in the patient's fibroblasts

NOTE Confidence: 0.966290021428571

00:20:14.198 --> 00:20:16.832 that didn't happen because the patients

NOTE Confidence: 0.966290021428571

00:20:16.832 --> 00:20:19.000 had increased alkaline phosphatase,

NOTE Confidence: 0.966290021428571

00:20:19.000 --> 00:20:20.480 then the alkaline phosphatase

NOTE Confidence: 0.966290021428571

00:20:20.480 --> 00:20:23.201 which is supposed to go to the

NOTE Confidence: 0.966290021428571

00:20:23.201 --> 00:20:25.781 surface of the cells and convert

NOTE Confidence: 0.966290021428571

00:20:25.781 --> 00:20:27.800 pyrophosphate into inorganic phosphate,

NOTE Confidence: 0.966290021428571

00:20:27.800 --> 00:20:30.542 that doesn't happen and instead you

NOTE Confidence: 0.966290021428571

00:20:30.542 --> 00:20:33.800 have too much alkaline phosphatase and

NOTE Confidence: 0.966290021428571

00:20:33.800 --> 00:20:37.272 the inorganic phosphate is formed and

NOTE Confidence: 0.966290021428571

00:20:37.272 --> 00:20:40.197 it enhances mineralization whereas the

NOTE Confidence: 0.966290021428571

00:20:40.200 --> 00:20:41.832 pyrophosphate normally inhibits and

NOTE Confidence: 0.966290021428571

00:20:41.832 --> 00:20:43.872 that accounts for the calcification

NOTE Confidence: 0.966290021428571

00:20:43.872 --> 00:20:46.159 in the vessels of these individuals.

NOTE Confidence: 0.950705813333333

00:20:48.480 --> 00:20:50.799 Here's another case,

NOTE Confidence: 0.950705813333333

00:20:50.800 --> 00:20:53.176 an 18 month old little girl who had

NOTE Confidence: 0.950705813333333

00:20:53.176 --> 00:20:55.597 failure to thrive and some intestinal

NOTE Confidence: 0.950705813333333

00:20:55.597 --> 00:20:58.231 problems with TTP and dependent etcetera.

NOTE Confidence: 0.950705813333333

00:20:58.240 --> 00:21:02.720 But her sort of claimed the fame for

NOTE Confidence: 0.950705813333333

00:21:02.720 --> 00:21:04.818 this particular disorder was she had

NOTE Confidence: 0.950705813333333

00:21:04.818 --> 00:21:06.588 hypopigmentation and the poor visual

NOTE Confidence: 0.950705813333333

00:21:06.588 --> 00:21:08.273 acuity that associates with it.

NOTE Confidence: 0.950705813333333

00:21:08.280 --> 00:21:10.488 Also had organomegaly, liver,

NOTE Confidence: 0.950705813333333

00:21:10.488 --> 00:21:13.344 spleen, kidney and storage there,

NOTE Confidence: 0.950705813333333

00:21:13.344 --> 00:21:16.800 and also had developmental delay with

NOTE Confidence: 0.950705813333333

00:21:16.800 --> 00:21:22.296 poor myelination and some infections too.

NOTE Confidence: 0.950705813333333

00:21:22.296 --> 00:21:25.182 But I'll mention this before telling you

NOTE Confidence: 0.950705813333333

00:21:25.182 --> 00:21:29.232 why she had no osteopatrosis and we'll

NOTE Confidence: 0.950705813333333

00:21:29.232 --> 00:21:33.438 keep that in mind when we see what she had.

NOTE Confidence: 0.950705813333333

00:21:33.440 --> 00:21:35.624 So here she is.

NOTE Confidence: 0.950705813333333

00:21:35.624 --> 00:21:38.280 She has cutaneous albinism

NOTE Confidence: 0.950705813333333

00:21:38.280 --> 00:21:41.400 and also white hair.

NOTE Confidence: 0.950705813333333

00:21:41.400 --> 00:21:42.960 She actually has some pigment in her iris,

NOTE Confidence: 0.950705813333333

00:21:42.960 --> 00:21:44.810 which is very unusual and

NOTE Confidence: 0.950705813333333

00:21:44.810 --> 00:21:45.920 delayed myelination here.

NOTE Confidence: 0.950705813333333

00:21:45.920 --> 00:21:48.839 And here's her storage in the liver,

NOTE Confidence: 0.950705813333333

00:21:48.840 --> 00:21:51.745 these big storage cells and in the

NOTE Confidence: 0.950705813333333

00:21:51.745 --> 00:21:53.960 duodenum and in the PMMS etcetera.

NOTE Confidence: 0.950705813333333

00:21:53.960 --> 00:21:55.120 And even in the fibroblast,

NOTE Confidence: 0.950705813333333

00:21:55.120 --> 00:21:56.908 she has bacols here.

NOTE Confidence: 0.950705813333333

00:21:56.908 --> 00:22:00.120 Bacols are better seen here as well.

NOTE Confidence: 0.950705813333333

00:22:00.120 --> 00:22:02.612 And then we found another patient who

NOTE Confidence: 0.950705813333333

00:22:02.612 --> 00:22:04.679 had essentially the same phenotype.

NOTE Confidence: 0.950705813333333

00:22:04.680 --> 00:22:07.176 So again, hypopigmentation,

NOTE Confidence: 0.950705813333333

00:22:07.176 --> 00:22:09.480 large liver, spleen,

NOTE Confidence: 0.950705813333333

00:22:09.480 --> 00:22:11.400 kidney and storage,

NOTE Confidence: 0.950705813333333

00:22:11.400 --> 00:22:13.960 developmental delay for myelination

NOTE Confidence: 0.950705813333333

00:22:13.960 --> 00:22:16.520 and no osteoporosis.

NOTE Confidence: 0.950705813333333

00:22:16.520 --> 00:22:19.478 Here's the fella and his dad,

NOTE Confidence: 0.950705813333333

00:22:19.480 --> 00:22:22.280 and here's the poor myelination.

NOTE Confidence: 0.950705813333333

00:22:22.280 --> 00:22:23.688 And here's the storage.

NOTE Confidence: 0.950705813333333

00:22:23.688 --> 00:22:27.640 And the storage and the storage fibroblast.

NOTE Confidence: 0.950705813333333

00:22:27.640 --> 00:22:27.995 Well,

NOTE Confidence: 0.950705813333333

00:22:27.995 --> 00:22:30.835 it turns out we found a de Novo

NOTE Confidence: 0.950705813333333

00:22:30.840 --> 00:22:35.040 mutation in a gene called CLCN 7,

NOTE Confidence: 0.950705813333333

00:22:35.040 --> 00:22:38.130 and CLCN 7 has a particular

NOTE Confidence: 0.950705813333333

00:22:38.130 --> 00:22:39.675 function in lysosomes.

NOTE Confidence: 0.950705813333333

00:22:39.680 --> 00:22:42.848 When the proton pump pumps hydrogen

NOTE Confidence: 0.950705813333333

00:22:42.848 --> 00:22:45.393 ions into a lysosome it does so

NOTE Confidence: 0.950705813333333

00:22:45.393 --> 00:22:47.586 for a long time and and then the

NOTE Confidence: 0.950705813333333

00:22:47.586 --> 00:22:49.421 hydrogen ions accumulate on the

NOTE Confidence: 0.950705813333333

00:22:49.421 --> 00:22:51.392 inner membrane of the lysosome

NOTE Confidence: 0.950705813333333

00:22:51.392 --> 00:22:53.552 and create an electric chemical

NOTE Confidence: 0.950705813333333

00:22:53.552 --> 00:22:55.810 gradient against which the next

NOTE Confidence: 0.950705813333333

00:22:55.810 --> 00:22:59.520 proton has a hard time getting in.

NOTE Confidence: 0.950705813333333

00:22:59.520 --> 00:23:04.078 So in order to dissipate that gradient

NOTE Confidence: 0.950705813333333

00:23:04.080 --> 00:23:07.880 God created CLCN 7 to put a counter

NOTE Confidence: 0.950705813333333

00:23:07.880 --> 00:23:10.718 ion chloride into the lysosome.

NOTE Confidence: 0.950705813333333

00:23:10.720 --> 00:23:14.290 So you if you don't have CLCN 7 you can't

NOTE Confidence: 0.950705813333333

00:23:14.378 --> 00:23:18.080 acidify the lysosome very well at at all.

NOTE Confidence: 0.950705813333333

00:23:18.080 --> 00:23:18.942 So chloride,

NOTE Confidence: 0.950705813333333

00:23:18.942 --> 00:23:21.097 This CLCN 7 provides the

NOTE Confidence: 0.950705813333333

00:23:21.097 --> 00:23:22.880 counter ion for this.

NOTE Confidence: 0.950705813333333

00:23:22.880 --> 00:23:25.124 And in fact there's a disease

NOTE Confidence: 0.950705813333333

00:23:25.124 --> 00:23:27.097 associated with loss of function

NOTE Confidence: 0.950705813333333

00:23:27.097 --> 00:23:29.515 by allelic mutations in CLCN 7.

NOTE Confidence: 0.950705813333333

00:23:29.520 --> 00:23:32.280 That is a disease called osteopatrosis.

NOTE Confidence: 0.950705813333333

00:23:32.280 --> 00:23:33.432 So in other words,

NOTE Confidence: 0.950705813333333

00:23:33.432 --> 00:23:35.160 the bone doesn't get broken down

NOTE Confidence: 0.950705813333333

00:23:35.160 --> 00:23:38.890 because the osteoclasts can't create

NOTE Confidence: 0.950705813333333

00:23:38.890 --> 00:23:42.726 the lacunae of acidic lysosomes to

NOTE Confidence: 0.950705813333333

00:23:42.726 --> 00:23:45.264 use the hydrolases to breakdown the

NOTE Confidence: 0.950705813333333

00:23:45.264 --> 00:23:47.999 bone so they have osteopetrosis.

NOTE Confidence: 0.950705813333333

00:23:48.000 --> 00:23:50.240 Again, loss of function bileelic.

NOTE Confidence: 0.950705813333333

00:23:50.240 --> 00:23:52.425 This was instead a mutation

NOTE Confidence: 0.950705813333333

00:23:52.425 --> 00:23:55.124 in a different spot which was

NOTE Confidence: 0.950705813333333

00:23:55.124 --> 00:23:56.840 monolelic and de Novo.

NOTE Confidence: 0.950705813333333

00:23:56.840 --> 00:23:58.200 So we posited that this

NOTE Confidence: 0.950705813333333

00:23:58.200 --> 00:23:59.560 is a gain of function.

NOTE Confidence: 0.950705813333333

00:23:59.560 --> 00:24:01.798 And our collaborator Joe Mendel and

NOTE Confidence: 0.950705813333333

00:24:01.800 --> 00:24:04.608 NANDS did patch clamp studies of

NOTE Confidence: 0.950705813333333

00:24:04.608 --> 00:24:07.047 xenoposol sites to demonstrate the

NOTE Confidence: 0.950705813333333

00:24:07.047 --> 00:24:09.497 chloride channel and the chloride

NOTE Confidence: 0.950705813333333

00:24:09.497 --> 00:24:11.457 movement across the membrane

NOTE Confidence: 0.950705813333333

00:24:11.536 --> 00:24:12.799 of these oocytes.

NOTE Confidence: 0.950705813333333

00:24:12.800 --> 00:24:14.599 When he put in the wild type,

NOTE Confidence: 0.950705813333333

00:24:14.600 --> 00:24:15.680 he got this much current.

NOTE Confidence: 0.950705813333333

00:24:15.680 --> 00:24:16.556 When he put in the mutant,

NOTE Confidence: 0.950705813333333

00:24:16.560 --> 00:24:18.000 he got this much current.

NOTE Confidence: 0.950705813333333

00:24:18.000 --> 00:24:21.252 And that increase in current was

NOTE Confidence: 0.950705813333333

00:24:21.252 --> 00:24:25.592 associated down here with more acid.

NOTE Confidence: 0.950705813333333

00:24:25.592 --> 00:24:27.440 In other words,

NOTE Confidence: 0.950705813333333

00:24:27.440 --> 00:24:29.568 hyperacidosis of the lysosome.

NOTE Confidence: 0.950705813333333

00:24:29.568 --> 00:24:32.760 Used fluorescent markers to demonstrate that.

NOTE Confidence: 0.950705813333333

00:24:32.760 --> 00:24:34.290 But you can see the difference

NOTE Confidence: 0.950705813333333

00:24:34.290 --> 00:24:35.310 in fluorescence in the

NOTE Confidence: 0.846789955833333

00:24:35.366 --> 00:24:38.130 pro band, the other pro band and

NOTE Confidence: 0.846789955833333

00:24:38.130 --> 00:24:41.068 the consequent decrease in pH

NOTE Confidence: 0.846789955833333

00:24:41.068 --> 00:24:45.278 really only a .2 or .3 units of pH,

NOTE Confidence: 0.846789955833333

00:24:45.280 --> 00:24:47.878 but that's it's a log scale.

NOTE Confidence: 0.846789955833333

00:24:47.880 --> 00:24:51.128 So that's a lot of more acid in

NOTE Confidence: 0.846789955833333

00:24:51.128 --> 00:24:53.838 these lysosomes of these individuals.

NOTE Confidence: 0.846789955833333

00:24:53.840 --> 00:24:56.376 So we're saying that this is a new

NOTE Confidence: 0.846789955833333

00:24:56.376 --> 00:24:58.005 disease associated with hyper acidity

NOTE Confidence: 0.846789955833333

00:24:58.005 --> 00:25:00.520 of the lysosomes and you can see why

NOTE Confidence: 0.846789955833333

00:25:00.520 --> 00:25:02.960 that would cause storage because the

NOTE Confidence: 0.846789955833333

00:25:02.960 --> 00:25:06.440 lysosomal hydrolases not only need acid,

NOTE Confidence: 0.846789955833333

00:25:06.440 --> 00:25:09.320 they needed the the right pH.

NOTE Confidence: 0.846789955833333

00:25:09.320 --> 00:25:13.757 Isn't a an optimal pH occur for these things,

NOTE Confidence: 0.846789955833333

00:25:13.760 --> 00:25:14.798 So it can't be too acid.

NOTE Confidence: 0.846789955833333

00:25:14.800 --> 00:25:15.920 It can't be not enough.

NOTE Confidence: 0.846789955833333

00:25:15.920 --> 00:25:17.198 Not only that,

NOTE Confidence: 0.846789955833333

00:25:17.198 --> 00:25:21.235 but this was a dominant disorder and we

NOTE Confidence: 0.846789955833333

00:25:21.235 --> 00:25:24.816 proved that by transfecting the mutant

NOTE Confidence: 0.846789955833333

00:25:24.816 --> 00:25:29.632 CLC on 7 gene into normal fibroblasts.

NOTE Confidence: 0.846789955833333

00:25:29.640 --> 00:25:31.130 So remember these normal fibroblasts

NOTE Confidence: 0.846789955833333

00:25:31.130 --> 00:25:33.152 is a normal contingent of CLC on 7.

NOTE Confidence: 0.846789955833333

00:25:33.152 --> 00:25:34.958 Now they've also got the the mutant

NOTE Confidence: 0.846789955833333

00:25:34.958 --> 00:25:37.034 and the mutant causes the accumulation

NOTE Confidence: 0.846789955833333

00:25:37.034 --> 00:25:39.119 of vesicles that you see here.

NOTE Confidence: 0.846789955833333

00:25:39.120 --> 00:25:43.035 So dominant disorder and then our

NOTE Confidence: 0.846789955833333

00:25:43.035 --> 00:25:46.653 people Rallu and May created a mouse

NOTE Confidence: 0.846789955833333

00:25:46.653 --> 00:25:50.865 knock in of the mouse paralogue of

NOTE Confidence: 0.846789955833333

00:25:50.865 --> 00:25:54.972 it's called CLCN 7 and those mice are

NOTE Confidence: 0.846789955833333

00:25:54.972 --> 00:25:58.346 a little bit hypo pigmented and they

NOTE Confidence: 0.846789955833333

00:25:58.346 --> 00:26:00.117 have the back rules and they have

NOTE Confidence: 0.846789955833333

00:26:00.117 --> 00:26:02.199 the storage in their liver etcetera.

NOTE Confidence: 0.846789955833333

00:26:02.200 --> 00:26:02.595 Well,

NOTE Confidence: 0.846789955833333

00:26:02.595 --> 00:26:04.965 one interesting issue is that you

NOTE Confidence: 0.846789955833333

00:26:04.965 --> 00:26:06.840 can actually alkalinize lysosomes.

NOTE Confidence: 0.846789955833333

00:26:06.840 --> 00:26:08.716 We knew this from the early studies

NOTE Confidence: 0.846789955833333

00:26:08.716 --> 00:26:10.718 of new fell etcetera and the way you

NOTE Confidence: 0.846789955833333

00:26:10.718 --> 00:26:13.000 can do it is by giving chloroquine.

NOTE Confidence: 0.846789955833333

00:26:13.000 --> 00:26:18.084 So we fed these folks fed chloroquine

NOTE Confidence: 0.846789955833333

00:26:18.084 --> 00:26:21.472 and lysotrac or red is an indication

NOTE Confidence: 0.846789955833333

00:26:21.472 --> 00:26:23.160 of lysosomal acidity.

NOTE Confidence: 0.846789955833333

00:26:23.160 --> 00:26:25.720 So all this red here and then you

NOTE Confidence: 0.846789955833333

00:26:25.720 --> 00:26:27.425 add more higher concentrations of

NOTE Confidence: 0.846789955833333

00:26:27.425 --> 00:26:29.555 chloroquine and the red goes away,

NOTE Confidence: 0.846789955833333

00:26:29.560 --> 00:26:31.610 meaning that you're now offering

NOTE Confidence: 0.846789955833333

00:26:31.610 --> 00:26:33.660 some alkalinization to the lysosomes

NOTE Confidence: 0.846789955833333

00:26:33.721 --> 00:26:35.809 and you can see that the pH actually

NOTE Confidence: 0.846789955833333

00:26:35.809 --> 00:26:38.000 goes up with increased chloroquine.

NOTE Confidence: 0.846789955833333

00:26:38.000 --> 00:26:38.424 Well,

NOTE Confidence: 0.846789955833333

00:26:38.424 --> 00:26:41.392 one the the physician for the patient

NOTE Confidence: 0.846789955833333

00:26:41.392 --> 00:26:43.856 from Ghana was Doctor Deborah de

NOTE Confidence: 0.846789955833333

00:26:43.856 --> 00:26:45.876 Salvatore in New Brunswick and

NOTE Confidence: 0.846789955833333

00:26:45.876 --> 00:26:48.992 she wrote a protocol to treat her

NOTE Confidence: 0.846789955833333

00:26:48.992 --> 00:26:50.312 patient with chloroquine.

NOTE Confidence: 0.846789955833333

00:26:50.320 --> 00:26:51.840 And when she did that,

NOTE Confidence: 0.846789955833333

00:26:51.840 --> 00:26:53.480 his kidney size decreased.

NOTE Confidence: 0.846789955833333

00:26:53.480 --> 00:26:55.120 He had more energy.

NOTE Confidence: 0.846789955833333

00:26:55.120 --> 00:26:56.560 He rolled over for the

NOTE Confidence: 0.846789955833333

00:26:56.560 --> 00:26:58.000 first time in his life.

NOTE Confidence: 0.846789955833333

00:26:58.000 --> 00:27:01.038 Both of our patients died their disease,

NOTE Confidence: 0.846789955833333

00:27:01.040 --> 00:27:03.230 but a number of other patients

NOTE Confidence: 0.846789955833333

00:27:03.230 --> 00:27:07.400 have appeared and we're trying to

NOTE Confidence: 0.846789955833333

00:27:07.400 --> 00:27:08.966 establish a protocol to treat them

NOTE Confidence: 0.846789955833333

00:27:08.966 --> 00:27:10.296 with the legal specific Aligos

NOTE Confidence: 0.846789955833333

00:27:10.296 --> 00:27:11.934 because this is a gain of function

NOTE Confidence: 0.846789955833333

00:27:11.934 --> 00:27:13.397 that maybe you could knock down.

NOTE Confidence: 0.843054013529412

00:27:16.640 --> 00:27:18.482 Another case of a couple of

NOTE Confidence: 0.843054013529412

00:27:18.482 --> 00:27:20.530 brothers who we saw early and

NOTE Confidence: 0.843054013529412

00:27:20.530 --> 00:27:22.400 they had lost some milestones,

NOTE Confidence: 0.843054013529412

00:27:22.400 --> 00:27:25.644 became a toxic and myoclonic, had seizures.

NOTE Confidence: 0.843054013529412

00:27:25.644 --> 00:27:28.060 One of them died and they had an

NOTE Confidence: 0.843054013529412

00:27:28.130 --> 00:27:30.218 MRI that showed a small cerebellum

NOTE Confidence: 0.843054013529412

00:27:30.218 --> 00:27:32.598 and we didn't know what they had.

NOTE Confidence: 0.843054013529412

00:27:32.600 --> 00:27:33.880 So here's the small cerebellum

NOTE Confidence: 0.843054013529412

00:27:33.880 --> 00:27:35.894 which you can see in the pro band

NOTE Confidence: 0.843054013529412

00:27:35.894 --> 00:27:37.476 compared to the mom and the dad.

NOTE Confidence: 0.843054013529412

00:27:37.480 --> 00:27:39.727 So we did an exome sequencing on

NOTE Confidence: 0.843054013529412

00:27:39.727 --> 00:27:42.106 the family and it turns out there

NOTE Confidence: 0.843054013529412

00:27:42.106 --> 00:27:44.116 are six members of the family.

NOTE Confidence: 0.843054013529412

00:27:44.120 --> 00:27:46.088 So we had the parents and we had

NOTE Confidence: 0.843054013529412

00:27:46.088 --> 00:27:47.680 two affected and two unaffected.

NOTE Confidence: 0.843054013529412

00:27:47.680 --> 00:27:50.158 And when you compare 1 exome

NOTE Confidence: 0.843054013529412

00:27:50.158 --> 00:27:51.397 with another exome,

NOTE Confidence: 0.843054013529412

00:27:51.400 --> 00:27:54.640 there'll usually be about 20,000 variants.

NOTE Confidence: 0.843054013529412

00:27:54.640 --> 00:27:56.439 So among all these family of six,

NOTE Confidence: 0.843054013529412

00:27:56.440 --> 00:28:00.106 there are 120,000 variants that were

NOTE Confidence: 0.843054013529412

00:28:00.106 --> 00:28:01.980 different and so we had to filter

NOTE Confidence: 0.843054013529412

00:28:01.980 --> 00:28:03.805 that down and we finally filtered it

NOTE Confidence: 0.843054013529412

00:28:03.805 --> 00:28:05.665 down to considering that this was

NOTE Confidence: 0.843054013529412

00:28:05.665 --> 00:28:07.665 going to be a a recessive disease

NOTE Confidence: 0.843054013529412

00:28:07.665 --> 00:28:09.360 because the parents were first cousins

NOTE Confidence: 0.843054013529412

00:28:09.360 --> 00:28:11.160 and shared 1/8 of their genes.

NOTE Confidence: 0.843054013529412

00:28:11.160 --> 00:28:12.870 So we're looking for a recessive

NOTE Confidence: 0.843054013529412

00:28:12.870 --> 00:28:14.916 disorder with the homozygous variant

NOTE Confidence: 0.843054013529412

00:28:14.916 --> 00:28:17.550 that we would call a mutation

NOTE Confidence: 0.843054013529412

00:28:17.628 --> 00:28:20.404 eventually found one in AFG 3L2.

NOTE Confidence: 0.843054013529412

00:28:20.404 --> 00:28:24.720 So homozygous for that and AFGL 3L2.

NOTE Confidence: 0.843054013529412

00:28:24.720 --> 00:28:28.110 AFG 3L2 is a very interesting

NOTE Confidence: 0.843054013529412

00:28:28.110 --> 00:28:30.836 mitochondrial protease that is important

NOTE Confidence: 0.843054013529412

00:28:30.836 --> 00:28:34.560 for the formation of axons in nerves,

NOTE Confidence: 0.843054013529412

00:28:34.560 --> 00:28:38.880 and this protein does two things.

NOTE Confidence: 0.843054013529412

00:28:38.880 --> 00:28:41.772 It forms a heterodimer with a

NOTE Confidence: 0.843054013529412

00:28:41.772 --> 00:28:44.221 protein called paraplegian and then

NOTE Confidence: 0.843054013529412

00:28:44.221 --> 00:28:46.837 it forms a homodimer with itself.

NOTE Confidence: 0.843054013529412

00:28:46.840 --> 00:28:49.440 And there were already diseases

NOTE Confidence: 0.843054013529412

00:28:49.440 --> 00:28:53.320 associated with AFG 3O2 and paraplegia.

NOTE Confidence: 0.843054013529412

00:28:53.320 --> 00:28:56.513 The paraplegian gene was a recessive

NOTE Confidence: 0.843054013529412

00:28:56.513 --> 00:28:59.012 hereditary ******* paraplegia

NOTE Confidence: 0.843054013529412

00:28:59.012 --> 00:29:01.160 and the AFG 3L2

NOTE Confidence: 0.774782711

00:29:03.240 --> 00:29:06.672 disorder was SCA 28 was a

NOTE Confidence: 0.774782711

00:29:06.672 --> 00:29:08.960 dominant spinal cerebellar ataxia,

NOTE Confidence: 0.774782711

00:29:08.960 --> 00:29:11.544 but this was the first occasion in which

NOTE Confidence: 0.774782711

00:29:11.544 --> 00:29:13.840 there were bioelic mutations in AFG 3L2.

NOTE Confidence: 0.774782711

00:29:13.840 --> 00:29:16.368 In other words, complete loss of function.

NOTE Confidence: 0.774782711

00:29:16.368 --> 00:29:18.928 So this protein could no

NOTE Confidence: 0.774782711

00:29:18.928 --> 00:29:20.781 longer react with itself.

NOTE Confidence: 0.774782711

00:29:20.781 --> 00:29:24.560 There were no good copies to form the

NOTE Confidence: 0.774782711

00:29:24.560 --> 00:29:27.675 homodimer and it can no longer react with

NOTE Confidence: 0.774782711

00:29:27.675 --> 00:29:29.448 paraplegion and form the heterodimer.

NOTE Confidence: 0.774782711

00:29:29.448 --> 00:29:30.640 So these patients,

NOTE Confidence: 0.774782711

00:29:30.640 --> 00:29:32.683 these boys had both diseases,

NOTE Confidence: 0.774782711

00:29:32.683 --> 00:29:36.091 they had both SBG 7 and SCA 28

NOTE Confidence: 0.774782711

00:29:36.091 --> 00:29:38.661 along with myoclinic epilepsy only

NOTE Confidence: 0.774782711

00:29:38.661 --> 00:29:41.680 patients in the world with that.

NOTE Confidence: 0.774782711

00:29:41.680 --> 00:29:46.360 So over the course of our work in the

NOTE Confidence: 0.774782711

00:29:46.360 --> 00:29:48.600 undiagnosed these program which is

NOTE Confidence: 0.774782711

00:29:48.694 --> 00:29:50.906 within the NIH intramural program,

NOTE Confidence: 0.774782711

00:29:50.906 --> 00:29:53.984 we have discovered 30 new disease

NOTE Confidence: 0.774782711

00:29:53.984 --> 00:29:56.114 gene associations and some of

NOTE Confidence: 0.774782711

00:29:56.114 --> 00:29:57.478 them are listed here.

NOTE Confidence: 0.774782711

00:29:57.480 --> 00:29:59.680 So the phenotype on the left and then

NOTE Confidence: 0.774782711

00:29:59.680 --> 00:30:02.319 the gene associated with it on the right.

NOTE Confidence: 0.774782711

00:30:02.320 --> 00:30:04.432 And obviously in order to prove

NOTE Confidence: 0.774782711

00:30:04.432 --> 00:30:06.760 that you have this association,

NOTE Confidence: 0.774782711

00:30:06.760 --> 00:30:08.040 you need to publish it,

NOTE Confidence: 0.774782711

00:30:08.040 --> 00:30:09.468 which means you need at least

NOTE Confidence: 0.774782711

00:30:09.468 --> 00:30:10.600 two cases to demonstrate it.

NOTE Confidence: 0.774782711

00:30:10.600 --> 00:30:12.118 And here are 15 other ones.

NOTE Confidence: 0.737925404545455

00:30:16.120 --> 00:30:18.456 Now I want to show you a phenotypic

NOTE Confidence: 0.737925404545455

00:30:18.456 --> 00:30:20.460 expansion because sometimes we discover

NOTE Confidence: 0.737925404545455

00:30:20.460 --> 00:30:23.365 new diseases and sometimes we discover a

NOTE Confidence: 0.737925404545455

00:30:23.365 --> 00:30:25.315 different expression of a known disease,

NOTE Confidence: 0.737925404545455

00:30:25.320 --> 00:30:27.273 and that's what we're going to show you here.

NOTE Confidence: 0.737925404545455

00:30:27.280 --> 00:30:31.198 This is a tube B4B tubulopathy.

NOTE Confidence: 0.737925404545455

00:30:31.200 --> 00:30:35.248 So you know, the microtubules transport

NOTE Confidence: 0.737925404545455

00:30:35.248 --> 00:30:38.510 things like small vesicles from near the

NOTE Confidence: 0.737925404545455

00:30:38.510 --> 00:30:40.514 nucleus to the plasma membrane, etcetera.

NOTE Confidence: 0.737925404545455

00:30:40.514 --> 00:30:43.346 So here's a little girl who's got some

NOTE Confidence: 0.737925404545455

00:30:43.346 --> 00:30:45.862 eye findings and some dysmorphisms

NOTE Confidence: 0.737925404545455

00:30:45.862 --> 00:30:47.950 and she's got hypophosphatemic

NOTE Confidence: 0.737925404545455

00:30:47.950 --> 00:30:51.078 rickets along with nephrocalcinosis.

NOTE Confidence: 0.737925404545455

00:30:51.080 --> 00:30:53.576 In fact, we documented renal tubular

NOTE Confidence: 0.737925404545455

00:30:53.576 --> 00:30:56.118 Fanconi syndrome in here along with

NOTE Confidence: 0.737925404545455

00:30:56.118 --> 00:30:58.532 hearing loss and her hypotonia and

NOTE Confidence: 0.737925404545455

00:30:58.532 --> 00:31:01.004 we found a de Novo heterozygous

NOTE Confidence: 0.737925404545455

00:31:01.004 --> 00:31:04.500 mutation in tube B4B and we eliminated

NOTE Confidence: 0.737925404545455

00:31:04.500 --> 00:31:08.560 all other causes of that we knew of

NOTE Confidence: 0.737925404545455

00:31:08.560 --> 00:31:10.360 renal tubular Franconi syndrome.

NOTE Confidence: 0.737925404545455

00:31:10.360 --> 00:31:12.040 Incidentally, a lot of this work

NOTE Confidence: 0.737925404545455

00:31:12.040 --> 00:31:14.000 was done by Jason McFadden here,

NOTE Confidence: 0.737925404545455

00:31:14.000 --> 00:31:15.600 who is matriculating into Yale

NOTE Confidence: 0.737925404545455

00:31:15.600 --> 00:31:16.880 Medical School next year.

NOTE Confidence: 0.737925404545455

00:31:16.880 --> 00:31:19.600 So we're all proud of him.

NOTE Confidence: 0.737925404545455

00:31:19.600 --> 00:31:22.508 And so the known diseases of tube B4B,

NOTE Confidence: 0.737925404545455

00:31:22.508 --> 00:31:24.836 the at least two phenotypes associated,

NOTE Confidence: 0.737925404545455

00:31:24.840 --> 00:31:27.199 one was up here with this mutation,

NOTE Confidence: 0.737925404545455

00:31:27.200 --> 00:31:30.714 the C1171 and this the 1172 etcetera

NOTE Confidence: 0.737925404545455

00:31:30.714 --> 00:31:33.329 and they all had the auditory

NOTE Confidence: 0.737925404545455

00:31:33.329 --> 00:31:35.879 dysfunction and some eye findings

NOTE Confidence: 0.737925404545455

00:31:35.879 --> 00:31:39.038 etcetera along with various other stuff.

NOTE Confidence: 0.737925404545455

00:31:39.040 --> 00:31:41.784 But none of the patients associated with

NOTE Confidence: 0.737925404545455

00:31:41.784 --> 00:31:44.716 these mutations had renal tubular Franconi

NOTE Confidence: 0.737925404545455

00:31:44.716 --> 00:31:46.960 syndrome or hypophosphatemic rickets.

NOTE Confidence: 0.737925404545455

00:31:46.960 --> 00:31:51.360 Ours was a different mutation.

NOTE Confidence: 0.737925404545455

00:31:51.360 --> 00:31:53.115 In order to understand how

NOTE Confidence: 0.737925404545455

00:31:53.115 --> 00:31:54.519 this might be occurring,

NOTE Confidence: 0.737925404545455

00:31:54.520 --> 00:31:57.640 we got help and collaboration from

NOTE Confidence: 0.737925404545455

00:31:57.640 --> 00:32:02.280 an expert in this in child health,

NOTE Confidence: 0.737925404545455

00:32:02.280 --> 00:32:05.598 and he taught us about microtubules.

NOTE Confidence: 0.737925404545455

00:32:05.600 --> 00:32:07.672 They start out as dimers of alpha

NOTE Confidence: 0.737925404545455

00:32:07.672 --> 00:32:08.560 and beta tubulin,

NOTE Confidence: 0.737925404545455

00:32:08.560 --> 00:32:10.840 and then they form lines,

NOTE Confidence: 0.737925404545455

00:32:10.840 --> 00:32:13.930 and then the lines line up and form

NOTE Confidence: 0.737925404545455

00:32:13.930 --> 00:32:15.220 essentially circles,

NOTE Confidence: 0.737925404545455

00:32:15.220 --> 00:32:17.800 which are really cylinders.

NOTE Confidence: 0.737925404545455

00:32:17.800 --> 00:32:21.839 And there's an edge that is growing.

NOTE Confidence: 0.737925404545455

00:32:21.840 --> 00:32:24.342 I'll show you that here the edge

NOTE Confidence: 0.737925404545455

00:32:24.342 --> 00:32:26.997 grows and then it recedes.

NOTE Confidence: 0.737925404545455

00:32:27.000 --> 00:32:29.480 And this growth and recession

NOTE Confidence: 0.737925404545455

00:32:29.480 --> 00:32:33.600 is critical for movement of

NOTE Confidence: 0.737925404545455

00:32:33.600 --> 00:32:36.000 vesicles along these microtubules.

NOTE Confidence: 0.737925404545455

00:32:36.000 --> 00:32:37.608 If you don't have this ability

NOTE Confidence: 0.737925404545455

00:32:37.608 --> 00:32:39.160 to grow and to recede,

NOTE Confidence: 0.737925404545455

00:32:39.160 --> 00:32:42.376 you can't move things and the

NOTE Confidence: 0.737925404545455

00:32:42.376 --> 00:32:44.520 microtubules don't form properly.

NOTE Confidence: 0.737925404545455

00:32:44.520 --> 00:32:49.079 So it turns out that there's a site on

NOTE Confidence: 0.737925404545455

00:32:49.079 --> 00:32:53.551 the tube B4B that is responsible for the

NOTE Confidence: 0.737925404545455

00:32:53.551 --> 00:32:56.758 microtubule assembly and disassembly.

NOTE Confidence: 0.737925404545455

00:32:56.760 --> 00:33:01.168 And that site is a site that binds

NOTE Confidence: 0.737925404545455

00:33:01.168 --> 00:33:07.640 GTP and has a GTPA that hydrolyzes

NOTE Confidence: 0.737925404545455

00:33:07.640 --> 00:33:10.360 the GTP to GDP.

NOTE Confidence: 0.737925404545455

00:33:10.360 --> 00:33:14.648 And that site is here and the

NOTE Confidence: 0.737925404545455

00:33:14.648 --> 00:33:16.968 mutations in previous cases are

NOTE Confidence: 0.737925404545455

00:33:16.968 --> 00:33:20.203 here and here having nothing to do

NOTE Confidence: 0.737925404545455

00:33:20.203 --> 00:33:22.574 with that Gtpa's activity site.

NOTE Confidence: 0.737925404545455

00:33:22.574 --> 00:33:25.562 But our patients mutation is right

NOTE Confidence: 0.737925404545455

00:33:25.562 --> 00:33:28.684 nearby and likely affected that Gtpa's

NOTE Confidence: 0.737925404545455

00:33:28.684 --> 00:33:32.548 activity and site and therefore impaired

NOTE Confidence: 0.737925404545455

00:33:32.548 --> 00:33:36.440 the disassembly of these microtubules.

NOTE Confidence: 0.737925404545455

00:33:36.440 --> 00:33:37.840 And there's evidence for that,

NOTE Confidence: 0.737925404545455

00:33:37.840 --> 00:33:40.308 biochemical evidence because when

NOTE Confidence: 0.737925404545455

00:33:40.308 --> 00:33:42.159 microtubules don't disassemble,

NOTE Confidence: 0.737925404545455

00:33:42.160 --> 00:33:44.890 they stay around longer and

NOTE Confidence: 0.737925404545455

00:33:44.890 --> 00:33:47.400 therefore they are modified and

NOTE Confidence: 0.737925404545455

00:33:47.400 --> 00:33:49.360 they're modified by acetylation.

NOTE Confidence: 0.737925404545455

00:33:49.360 --> 00:33:51.620 So when you measure total

NOTE Confidence: 0.737925404545455

00:33:51.620 --> 00:33:53.880 turbulent by a western blot,

NOTE Confidence: 0.737925404545455

00:33:53.880 --> 00:33:55.768 you see that the control and the probe

NOTE Confidence: 0.737925404545455

00:33:55.768 --> 00:33:57.480 band have the same amount roughly,

NOTE Confidence: 0.737925404545455

00:33:57.480 --> 00:34:00.078 but when you measure accelerated tubulin,

NOTE Confidence: 0.737925404545455

00:34:00.080 --> 00:34:01.988 the probe band has much more

NOTE Confidence: 0.737925404545455

00:34:01.988 --> 00:34:03.824 because the stuff is sitting

NOTE Confidence: 0.737925404545455

00:34:03.824 --> 00:34:05.800 around not being disassembled.

NOTE Confidence: 0.737925404545455

00:34:05.800 --> 00:34:07.896 This is a little bit to me like

NOTE Confidence: 0.737925404545455

00:34:07.896 --> 00:34:09.279 collagen being over modified.

NOTE Confidence: 0.737925404545455

00:34:09.280 --> 00:34:11.359 When there are variants and it stays,

NOTE Confidence: 0.28811988

00:34:11.360 --> 00:34:15.648 it has more time to be modified anyway.

NOTE Confidence: 0.28811988

00:34:15.648 --> 00:34:17.668 This indicates that the disassembly

NOTE Confidence: 0.28811988

00:34:17.668 --> 00:34:19.914 did not occur properly and leads

NOTE Confidence: 0.28811988

00:34:19.914 --> 00:34:21.858 us to the hypothesis for the

NOTE Confidence: 0.28811988

00:34:21.858 --> 00:34:23.838 renal tubular Franconi syndrome,

NOTE Confidence: 0.28811988

00:34:23.840 --> 00:34:28.528 namely that these tubules in renal

NOTE Confidence: 0.28811988

00:34:28.528 --> 00:34:30.788 tubular cells in proximal tubular

NOTE Confidence: 0.28811988

00:34:30.788 --> 00:34:35.824 cells move vesicles which contain

NOTE Confidence: 0.28811988

00:34:35.824 --> 00:34:40.642 phosphate transporters like SLC 34A3.

NOTE Confidence: 0.28811988

00:34:40.642 --> 00:34:42.447 And those transporters in the

NOTE Confidence: 0.28811988

00:34:42.447 --> 00:34:44.856 vesicles need to be moved to the

NOTE Confidence: 0.28811988

00:34:44.856 --> 00:34:46.431 plasma membrane of the tubules

NOTE Confidence: 0.28811988

00:34:46.431 --> 00:34:49.064 in order for them to function to

NOTE Confidence: 0.28811988

00:34:49.064 --> 00:34:51.340 reabsorb phosphate back into the body.

NOTE Confidence: 0.28811988

00:34:51.340 --> 00:34:54.070 And when that doesn't occur because there's

NOTE Confidence: 0.28811988

00:34:54.070 --> 00:34:56.759 no disassembly of the microtubules,

NOTE Confidence: 0.28811988

00:34:56.760 --> 00:34:58.878 the stuff the vesicles don't move,

NOTE Confidence: 0.28811988

00:34:58.880 --> 00:35:00.931 the transporter is not moved to the

NOTE Confidence: 0.28811988

00:35:00.931 --> 00:35:03.199 plasma membrane and these individuals cannot,

NOTE Confidence: 0.792757147272727

00:35:05.480 --> 00:35:07.440 cannot reabsorb their phosphate.

NOTE Confidence: 0.792757147272727

00:35:07.440 --> 00:35:10.880 So we told the family about this.

NOTE Confidence: 0.792757147272727

00:35:10.880 --> 00:35:12.400 It had been 10 years.

NOTE Confidence: 0.792757147272727

00:35:12.400 --> 00:35:13.912 We'd seen the family, but kept working

NOTE Confidence: 0.792757147272727

00:35:13.912 --> 00:35:15.637 on it and they were very pleased.

NOTE Confidence: 0.792757147272727

00:35:15.640 --> 00:35:18.475 And that's Jason. OK.

NOTE Confidence: 0.792757147272727

00:35:18.475 --> 00:35:20.675 So I would say that first of all,

NOTE Confidence: 0.792757147272727

00:35:20.680 --> 00:35:22.030 collaboration is important.

NOTE Confidence: 0.792757147272727

00:35:22.030 --> 00:35:24.730 This is possibly a mechanism for

NOTE Confidence: 0.792757147272727

00:35:24.730 --> 00:35:27.130 hypophosphatemic rickets and it was a great

NOTE Confidence: 0.792757147272727

00:35:27.130 --> 00:35:29.040 learning experience for for everybody.

NOTE Confidence: 0.792757147272727

00:35:29.040 --> 00:35:32.848 I'm going to quickly go through some

NOTE Confidence: 0.792757147272727

00:35:32.848 --> 00:35:34.925 diagnosis to demonstrate the unusual

NOTE Confidence: 0.792757147272727

00:35:34.925 --> 00:35:37.557 nature of the diagnosis that we make.

NOTE Confidence: 0.792757147272727

00:35:37.560 --> 00:35:40.638 Here are some that are we would call rare

NOTE Confidence: 0.792757147272727

00:35:40.640 --> 00:35:42.920 and I have like several slides of this.

NOTE Confidence: 0.792757147272727

00:35:42.920 --> 00:35:44.480 So I'm going through these fast.

NOTE Confidence: 0.792757147272727

00:35:44.480 --> 00:35:46.840 You don't have to actually look at any

NOTE Confidence: 0.792757147272727

00:35:46.840 --> 00:35:48.892 of these unless you find it of interest.

NOTE Confidence: 0.792757147272727

00:35:48.892 --> 00:35:50.360 But you see five in the world,

NOTE Confidence: 0.792757147272727

00:35:50.360 --> 00:35:51.440 six families in the world,

NOTE Confidence: 0.792757147272727

00:35:51.440 --> 00:35:52.480 20 families in the world,

NOTE Confidence: 0.792757147272727

00:35:52.480 --> 00:35:52.793 etcetera.

NOTE Confidence: 0.792757147272727

00:35:52.793 --> 00:35:54.984 Really unusual stuff because we get our

NOTE Confidence: 0.792757147272727

00:35:54.984 --> 00:35:56.917 patients from major medical centers that

NOTE Confidence: 0.792757147272727

00:35:56.917 --> 00:35:58.795 have already worked up the patients,

NOTE Confidence: 0.792757147272727

00:35:58.800 --> 00:36:03.571 you know really a lot and more diagnosis.

NOTE Confidence: 0.792757147272727

00:36:03.571 --> 00:36:06.691 I generally say that if you know

NOTE Confidence: 0.792757147272727

00:36:06.691 --> 00:36:08.953 all or almost all these diagnosis,

NOTE Confidence: 0.792757147272727

00:36:08.960 --> 00:36:10.200 you should get a life.

NOTE Confidence: 0.857775338333333

00:36:13.760 --> 00:36:15.716 Even geneticists will not know most,

NOTE Confidence: 0.857775338333333

00:36:15.720 --> 00:36:18.168 most of these in general and

NOTE Confidence: 0.857775338333333

00:36:18.168 --> 00:36:19.800 some the recent diagnosis.

NOTE Confidence: 0.857775338333333

00:36:19.800 --> 00:36:21.700 Yeah, I don't want to waste a lot of time

NOTE Confidence: 0.857775338333333

00:36:21.751 --> 00:36:24.580 on this but a lot of and then a couple

NOTE Confidence: 0.857775338333333

00:36:24.580 --> 00:36:26.955 of cases of personalized treatment.

NOTE Confidence: 0.857775338333333

00:36:26.960 --> 00:36:29.273 This is a 12 year old girl who had

NOTE Confidence: 0.857775338333333

00:36:29.273 --> 00:36:31.568 these exostoses and you can see it's

NOTE Confidence: 0.857775338333333

00:36:31.568 --> 00:36:34.052 not pleasant and you can see it with

NOTE Confidence: 0.857775338333333

00:36:34.052 --> 00:36:37.906 the arrow here and turns out she

NOTE Confidence: 0.857775338333333

00:36:37.906 --> 00:36:39.594 had familial tumoral calcinosis,

NOTE Confidence: 0.857775338333333

00:36:39.600 --> 00:36:41.673 which I know you know about time,

NOTE Confidence: 0.857775338333333

00:36:41.673 --> 00:36:44.628 but this is an FGF deficiency

NOTE Confidence: 0.857775338333333

00:36:44.628 --> 00:36:48.744 because FGF is a hormone that causes

NOTE Confidence: 0.857775338333333

00:36:48.744 --> 00:36:52.477 phosphate to be excreted in the urine.

NOTE Confidence: 0.857775338333333

00:36:52.480 --> 00:36:55.612 And if you don't have FGF you you

NOTE Confidence: 0.857775338333333

00:36:55.612 --> 00:36:57.688 instead reabsorb the phosphate and you

NOTE Confidence: 0.857775338333333

00:36:57.688 --> 00:37:00.280 have a lot of phosphate inside you.

NOTE Confidence: 0.857775338333333

00:37:00.280 --> 00:37:03.616 So an FGF deficiency will cause a high

NOTE Confidence: 0.857775338333333

00:37:03.616 --> 00:37:05.439 tubular reabsorption of phosphate.

NOTE Confidence: 0.857775338333333

00:37:05.440 --> 00:37:07.080 But you see here in the fourth line,

NOTE Confidence: 0.857775338333333

00:37:07.080 --> 00:37:08.776 fifth line or something,

NOTE Confidence: 0.857775338333333

00:37:08.776 --> 00:37:11.769 it's 96% or so and it it should

NOTE Confidence: 0.857775338333333

00:37:11.769 --> 00:37:14.654 be probably less than 80% or so.

NOTE Confidence: 0.857775338333333

00:37:14.654 --> 00:37:18.203 So we know that mutations in this

NOTE Confidence: 0.857775338333333

00:37:18.203 --> 00:37:21.560 Henacetyl galactosamineal transferase

NOTE Confidence: 0.857775338333333

00:37:21.560 --> 00:37:25.660 which puts an anaceto group on to FTF 23,

NOTE Confidence: 0.857775338333333

00:37:25.660 --> 00:37:26.520 see here.

NOTE Confidence: 0.857775338333333

00:37:26.520 --> 00:37:28.240 These are the anaceto

NOTE Confidence: 0.853328965

00:37:30.440 --> 00:37:31.720 galactosamineal residues

NOTE Confidence: 0.853328965

00:37:31.720 --> 00:37:35.136 along with sugars on FTF 23.

NOTE Confidence: 0.853328965

00:37:35.136 --> 00:37:37.704 These protect FTF 23 from being

NOTE Confidence: 0.853328965

00:37:37.704 --> 00:37:40.340 broken down and if you don't have

NOTE Confidence: 0.853328965

00:37:40.340 --> 00:37:42.590 that enzyme to put on then you

NOTE Confidence: 0.853328965

00:37:42.590 --> 00:37:44.000 don't have the protection and then

NOTE Confidence: 0.853328965

00:37:44.000 --> 00:37:47.390 the FTF 23 gets broken down and

NOTE Confidence: 0.853328965

00:37:47.390 --> 00:37:49.264 becomes inactive and essentially

NOTE Confidence: 0.853328965

00:37:49.264 --> 00:37:51.952 that's this is the mutation just

NOTE Confidence: 0.853328965

00:37:51.952 --> 00:37:54.360 showing that and showing that there

NOTE Confidence: 0.853328965

00:37:54.360 --> 00:37:58.088 was a lot of C terminal meaning

NOTE Confidence: 0.853328965

00:37:58.088 --> 00:38:01.120 broken down FTF 23 that caused this.

NOTE Confidence: 0.853328965

00:38:01.120 --> 00:38:03.577 So we're able to treat with debulking

NOTE Confidence: 0.853328965

00:38:03.577 --> 00:38:06.011 and a low phosphate diet etcetera

NOTE Confidence: 0.853328965

00:38:06.011 --> 00:38:07.925 and also an anti-inflammatory.

NOTE Confidence: 0.853328965

00:38:07.925 --> 00:38:12.160 So there was treatment associated with this.

NOTE Confidence: 0.853328965

00:38:12.160 --> 00:38:14.880 A second example of taking a rare disease,

NOTE Confidence: 0.853328965

00:38:14.880 --> 00:38:16.632 making a diagnosis and being able

NOTE Confidence: 0.853328965

00:38:16.632 --> 00:38:19.052 to treat is this 14 year old from

NOTE Confidence: 0.853328965

00:38:19.052 --> 00:38:20.840 Nigeria whom we didn't see because

NOTE Confidence: 0.853328965

00:38:20.840 --> 00:38:21.920 we couldn't get her over here.

NOTE Confidence: 0.853328965

00:38:21.920 --> 00:38:24.616 But also we we got her DNA etcetera

NOTE Confidence: 0.853328965

00:38:24.616 --> 00:38:27.330 and she had a lot of fractures

NOTE Confidence: 0.853328965

00:38:27.330 --> 00:38:29.774 and rickets and was treated with

NOTE Confidence: 0.853328965

00:38:29.774 --> 00:38:32.893 surgery and vitamin D here her,

NOTE Confidence: 0.853328965

00:38:32.893 --> 00:38:36.705 her X-rays and here she is spending

NOTE Confidence: 0.853328965

00:38:36.705 --> 00:38:39.520 most of her life in casts etcetera.

NOTE Confidence: 0.853328965

00:38:39.520 --> 00:38:43.420 And so we knew that there was

NOTE Confidence: 0.853328965

00:38:43.420 --> 00:38:44.800 a differential for the rickets

NOTE Confidence: 0.853328965

00:38:44.861 --> 00:38:46.477 including vitamin D deficiency,

NOTE Confidence: 0.853328965

00:38:46.480 --> 00:38:48.144 hypophosphatemia and metabolic acidosis.

NOTE Confidence: 0.853328965

00:38:48.144 --> 00:38:51.639 We got our labs showed the low phosphorus,

NOTE Confidence: 0.853328965

00:38:51.640 --> 00:38:54.034 the high up phos, it's a bone,

NOTE Confidence: 0.853328965

00:38:54.040 --> 00:38:54.856 bone breakdown,

NOTE Confidence: 0.853328965

00:38:54.856 --> 00:38:57.712 but you also had low serum bicarb

NOTE Confidence: 0.853328965

00:38:57.712 --> 00:38:59.377 and low serum potassium.

NOTE Confidence: 0.853328965

00:38:59.377 --> 00:39:02.962 So we got our DNA and we found

NOTE Confidence: 0.853328965

00:39:02.962 --> 00:39:08.052 the mutation in SLC 4A1 which is

NOTE Confidence: 0.853328965

00:39:08.052 --> 00:39:10.573 a transporter for chloride and

NOTE Confidence: 0.853328965

00:39:10.573 --> 00:39:13.159 bicarbonate in the distal renal tubule

NOTE Confidence: 0.853328965

00:39:13.160 --> 00:39:15.813 and it means that the treatment for

NOTE Confidence: 0.853328965

00:39:15.813 --> 00:39:17.921 her instead is alkali replacement

NOTE Confidence: 0.853328965

00:39:17.921 --> 00:39:20.603 and potassium and not more vitamin

NOTE Confidence: 0.853328965

00:39:20.603 --> 00:39:23.320 D and surgeries all the time.

NOTE Confidence: 0.853328965

00:39:23.320 --> 00:39:26.200 I think this is the final case.

NOTE Confidence: 0.853328965

00:39:26.200 --> 00:39:28.472 I'm going to show you a 22 year

NOTE Confidence: 0.853328965

00:39:28.472 --> 00:39:30.080 old woman with dystonia.

NOTE Confidence: 0.853328965

00:39:30.080 --> 00:39:32.516 And when she was in grade school,

NOTE Confidence: 0.853328965

00:39:32.520 --> 00:39:34.800 her teacher, she would grip her hand like,

NOTE Confidence: 0.853328965

00:39:34.800 --> 00:39:35.832 like a pen,

NOTE Confidence: 0.853328965

00:39:35.832 --> 00:39:37.552 like like this because she

NOTE Confidence: 0.853328965

00:39:37.552 --> 00:39:39.319 had dystonia in her fingers.

NOTE Confidence: 0.853328965

00:39:39.320 --> 00:39:40.958 Teachers, you know, holler at her,

NOTE Confidence: 0.853328965

00:39:40.960 --> 00:39:42.432 that's not the way to hold a pen, etcetera.

NOTE Confidence: 0.853328965

00:39:42.432 --> 00:39:43.680 She couldn't help it.

NOTE Confidence: 0.853328965

00:39:43.680 --> 00:39:45.528 And later she had trouble with her

NOTE Confidence: 0.853328965

00:39:45.528 --> 00:39:47.612 gait because of dysonia, you know,

NOTE Confidence: 0.853328965

00:39:47.612 --> 00:39:49.236 muscles clenching like this.

NOTE Confidence: 0.853328965

00:39:49.240 --> 00:39:51.440 But mainly she had problem with her tongue.

NOTE Confidence: 0.853328965

00:39:51.440 --> 00:39:52.548 She couldn't eat properly.

NOTE Confidence: 0.853328965

00:39:52.548 --> 00:39:54.480 She lost weight down to 80 lbs.

NOTE Confidence: 0.853328965

00:39:54.480 --> 00:39:56.720 She couldn't speak properly, etcetera.

NOTE Confidence: 0.853328965

00:39:56.720 --> 00:40:00.394 And we found a monolithic mutation in KMT 2B,

NOTE Confidence: 0.853328965

00:40:00.394 --> 00:40:03.376 which is a histone lysine methyl

NOTE Confidence: 0.853328965

00:40:03.376 --> 00:40:04.996 transferase and we didn't know

NOTE Confidence: 0.853328965

00:40:04.996 --> 00:40:06.670 that there was an association with

NOTE Confidence: 0.853328965

00:40:06.724 --> 00:40:08.608 this disease at the time, but.

NOTE Confidence: 0.853328965

00:40:08.608 --> 00:40:10.880 Because we were sharing,

NOTE Confidence: 0.853328965

00:40:10.880 --> 00:40:13.029 we put this on a website that

NOTE Confidence: 0.853328965

00:40:13.029 --> 00:40:14.280 other people could see.

NOTE Confidence: 0.853328965

00:40:14.280 --> 00:40:17.560 One of those people was Doctor Manju Korean,

NOTE Confidence: 0.853328965

00:40:17.560 --> 00:40:20.360 who ran a dystonia clinic in London.

NOTE Confidence: 0.853328965

00:40:20.360 --> 00:40:24.200 And she called me up one day and said,

NOTE Confidence: 0.853328965

00:40:24.200 --> 00:40:25.056 you know,

NOTE Confidence: 0.853328965

00:40:25.056 --> 00:40:28.313 I have 20 patients with KMT 2B mutations,

NOTE Confidence: 0.853328965

00:40:28.313 --> 00:40:30.539 and five of them we've treated

NOTE Confidence: 0.853328965

00:40:30.539 --> 00:40:32.598 with deep brain stimulation.

NOTE Confidence: 0.853328965

00:40:32.600 --> 00:40:35.320 So we work together somewhat.

NOTE Confidence: 0.853328965

00:40:35.320 --> 00:40:37.280 And then found another patient.

NOTE Confidence: 0.853328965

00:40:37.280 --> 00:40:38.780 Doctor Soldadas is a neurologist

NOTE Confidence: 0.853328965

00:40:38.780 --> 00:40:40.560 that saw this 20 year old,

NOTE Confidence: 0.853328965

00:40:40.560 --> 00:40:41.820 very similar history to the one

NOTE Confidence: 0.853328965

00:40:41.820 --> 00:40:42.880 that I just showed you.

NOTE Confidence: 0.853328965

00:40:42.880 --> 00:40:45.316 This 20 year old had clumsiness,

NOTE Confidence: 0.778978008181818

00:40:45.320 --> 00:40:47.405 poor Gait, couldn't speak properly

NOTE Confidence: 0.778978008181818

00:40:47.405 --> 00:40:50.040 because of dystonia on her tongue.

NOTE Confidence: 0.778978008181818

00:40:50.040 --> 00:40:51.960 She couldn't write properly,

NOTE Confidence: 0.778978008181818

00:40:51.960 --> 00:40:54.520 treated with Baclofen, etcetera,

NOTE Confidence: 0.778978008181818

00:40:54.520 --> 00:40:59.320 etcetera. And here she is. Yes,

NOTE Confidence: 0.5538232

00:41:01.920 --> 00:41:06.120 the normal cognition, normal adultion,

NOTE Confidence: 0.5538232

00:41:06.120 --> 00:41:08.520 can't move properly. Lying in bed,

NOTE Confidence: 0.951989613333333

00:41:09.200 --> 00:41:10.118 able to signal,

NOTE Confidence: 0.770644154

00:41:12.560 --> 00:41:14.600 able to learn by signaling,

NOTE Confidence: 0.507671825

00:41:35.360 --> 00:41:35.920 Doing that with our

NOTE Confidence: 0.76939710875

00:41:51.220 --> 00:41:52.940 I don't know who this Taylor Swift is,

NOTE Confidence: 0.76939710875

00:41:52.940 --> 00:41:56.660 but she apparently likes a song of hers.

NOTE Confidence: 0.76939710875

00:41:56.660 --> 00:41:58.788 In any event, we found that this young

NOTE Confidence: 0.76939710875

00:41:58.788 --> 00:42:01.828 lady also had a de Novo KMT 2B mutation,

NOTE Confidence: 0.76939710875

00:42:01.828 --> 00:42:03.556 therefore recommended treatment

NOTE Confidence: 0.76939710875

00:42:03.556 --> 00:42:05.860 with deep brain stimulator.

NOTE Confidence: 0.76939710875

00:42:05.860 --> 00:42:10.040 And here she is after the

NOTE Confidence: 0.76939710875

00:42:10.040 --> 00:42:11.060 deep brain stimulation.

NOTE Confidence: 0.704823704545455

00:42:13.560 --> 00:42:15.648 And I I I guess maybe I don't have

NOTE Confidence: 0.704823704545455

00:42:15.648 --> 00:42:18.104 to sort of emphasize how important

NOTE Confidence: 0.704823704545455

00:42:18.104 --> 00:42:20.484 small increments and this maybe

NOTE Confidence: 0.704823704545455

00:42:20.484 --> 00:42:22.533 not as even a small increment.

NOTE Confidence: 0.704823704545455

00:42:22.533 --> 00:42:24.805 But when you have someone who's so

NOTE Confidence: 0.704823704545455

00:42:24.805 --> 00:42:26.410 devastated that the activities of

NOTE Confidence: 0.704823704545455

00:42:26.467 --> 00:42:28.745 daily living are so difficult for not

NOTE Confidence: 0.704823704545455

00:42:28.745 --> 00:42:30.880 only the patient but for the family,

NOTE Confidence: 0.704823704545455

00:42:30.880 --> 00:42:36.240 this was transformational for this family.

NOTE Confidence: 0.704823704545455

00:42:36.240 --> 00:42:38.240 And why did it occur?

NOTE Confidence: 0.704823704545455

00:42:38.240 --> 00:42:40.280 I mean, she can walk steps.

NOTE Confidence: 0.68121346875

00:42:43.040 --> 00:42:45.440 You know, I'm going to go on here.

NOTE Confidence: 0.68121346875

00:42:45.440 --> 00:42:49.605 But it occurred because we shared

NOTE Confidence: 0.68121346875

00:42:49.605 --> 00:42:51.958 something and someone else shared with us.

NOTE Confidence: 0.8750436725

00:42:54.240 --> 00:42:56.120 OK, so a couple other things we do.

NOTE Confidence: 0.8750436725

00:42:56.120 --> 00:42:58.448 We have rounds on Thursday mornings

NOTE Confidence: 0.8750436725

00:42:58.448 --> 00:43:00.880 and that for basically people between

NOTE Confidence: 0.8750436725

00:43:00.880 --> 00:43:03.395 college and medical school or Graduate

NOTE Confidence: 0.8750436725

00:43:03.395 --> 00:43:05.837 School and present cases in person,

NOTE Confidence: 0.8750436725

00:43:05.840 --> 00:43:07.556 journal club and stuff like that.

NOTE Confidence: 0.8750436725

00:43:07.560 --> 00:43:11.928 In 2014, as Yahoo we mentioned,

NOTE Confidence: 0.8750436725

00:43:11.928 --> 00:43:14.008 we expanded to the Undiagnosed

NOTE Confidence: 0.8750436725

00:43:14.008 --> 00:43:17.640 Diseases Network, which is a national

NOTE Confidence: 0.8750436725

00:43:17.640 --> 00:43:20.360 consortium with 7 clinical sites,

NOTE Confidence: 0.8750436725

00:43:20.360 --> 00:43:23.240 a coordinating center, sequencing cores,

NOTE Confidence: 0.8750436725

00:43:23.240 --> 00:43:25.556 a metabolomics core model,

NOTE Confidence: 0.8750436725

00:43:25.556 --> 00:43:29.030 orchism screening center that does largely

NOTE Confidence: 0.8750436725

00:43:29.115 --> 00:43:32.637 Drosophila and Zebrafish and a repository.

NOTE Confidence: 0.8750436725

00:43:32.640 --> 00:43:34.512 I'm Pi of the protocol because

NOTE Confidence: 0.8750436725

00:43:34.512 --> 00:43:35.760 it's the research protocol.

NOTE Confidence: 0.8750436725

00:43:35.760 --> 00:43:38.714 Every patient enrolled as a research patient.

NOTE Confidence: 0.8750436725

00:43:38.720 --> 00:43:41.996 So we do the genetics especially

NOTE Confidence: 0.8750436725

00:43:42.000 --> 00:43:44.520 and expanded to 11 sites,

NOTE Confidence: 0.8750436725

00:43:44.520 --> 00:43:45.290 extramural sites,

NOTE Confidence: 0.8750436725

00:43:45.290 --> 00:43:47.600 the UDP and the interim program

NOTE Confidence: 0.8750436725

00:43:47.600 --> 00:43:49.519 is part of that as well.

NOTE Confidence: 0.8750436725

00:43:49.520 --> 00:43:55.464 And that group saw almost 7000 applications

NOTE Confidence: 0.8750436725

00:43:55.464 --> 00:44:00.144 and almost 2800 evaluated almost 2400

NOTE Confidence: 0.8750436725

00:44:00.144 --> 00:44:02.784 individuals made over 700 diagnosis

NOTE Confidence: 0.8750436725

00:44:02.784 --> 00:44:06.160 etcetera published a lot of papers in 2014.

NOTE Confidence: 0.8750436725

00:44:06.160 --> 00:44:11.408 We also expanded to UDP sites around

NOTE Confidence: 0.8750436725

00:44:11.408 --> 00:44:14.400 the world where the NIHUDP would

NOTE Confidence: 0.8750436725

00:44:14.400 --> 00:44:17.724 served as a model and established the

NOTE Confidence: 0.8750436725

00:44:17.724 --> 00:44:19.916 Undiagnosed Disease Network International,

NOTE Confidence: 0.8750436725

00:44:19.920 --> 00:44:21.720 which has a website,

NOTE Confidence: 0.8750436725

00:44:21.720 --> 00:44:23.520 a charter committees etcetera.

NOTE Confidence: 0.8750436725

00:44:23.520 --> 00:44:25.188 We've had 12 meetings,

NOTE Confidence: 0.8750436725

00:44:25.188 --> 00:44:27.273 Last one was in Tbilisi,

NOTE Confidence: 0.8750436725

00:44:27.280 --> 00:44:27.766 Georgia,

NOTE Confidence: 0.8750436725

00:44:27.766 --> 00:44:30.196 next one is in Seoul,

NOTE Confidence: 0.8750436725

00:44:30.200 --> 00:44:34.024 Korea and have new initiatives

NOTE Confidence: 0.8750436725

00:44:34.024 --> 00:44:36.048 including a diagnostics working

NOTE Confidence: 0.8750436725

00:44:36.048 --> 00:44:38.300 group and a low and middle income

NOTE Confidence: 0.8750436725

00:44:38.300 --> 00:44:39.869 countries working group that has

NOTE Confidence: 0.8750436725

00:44:39.869 --> 00:44:41.639 representatives all around the world.

NOTE Confidence: 0.8750436725

00:44:41.640 --> 00:44:44.976 And that working group is collaborating

NOTE Confidence: 0.8750436725

00:44:44.976 --> 00:44:46.960 with the Wilhelm Foundation.

NOTE Confidence: 0.8750436725

00:44:46.960 --> 00:44:49.488 Wilhelm Foundation is dedicated

NOTE Confidence: 0.8750436725

00:44:49.488 --> 00:44:53.830 to the promotion of undiagnosed

NOTE Confidence: 0.8750436725

00:44:53.830 --> 00:44:55.950 diseases programs throughout the

NOTE Confidence: 0.8750436725

00:44:55.950 --> 00:44:57.995 world because Elaine Cedaroth,

NOTE Confidence: 0.8750436725

00:44:57.995 --> 00:45:00.520 who founded this with her

NOTE Confidence: 0.8750436725

00:45:00.520 --> 00:45:02.639 husband along with the UDP.

NOTE Confidence: 0.8750436725

00:45:02.640 --> 00:45:03.316 In 2014,

NOTE Confidence: 0.8750436725

00:45:03.316 --> 00:45:05.682 she came to my laboratory and wanted

NOTE Confidence: 0.8750436725

00:45:05.682 --> 00:45:08.131 to have this Wilhelm Foundation

NOTE Confidence: 0.8750436725

00:45:08.131 --> 00:45:10.680 founded because she had three children

NOTE Confidence: 0.8750436725

00:45:10.680 --> 00:45:13.700 who all died of an undiagnosed

NOTE Confidence: 0.8750436725

00:45:13.700 --> 00:45:17.160 neurological disease in childhood.

NOTE Confidence: 0.8750436725

00:45:17.160 --> 00:45:19.799 So the Wilhelm Foundation and the UD

NOTE Confidence: 0.8750436725

00:45:19.799 --> 00:45:22.708 and I working groups got together

NOTE Confidence: 0.8750436725

00:45:22.708 --> 00:45:25.393 to establish the Champions program

NOTE Confidence: 0.8750436725

00:45:25.400 --> 00:45:28.400 which I have so far identified

NOTE Confidence: 0.8750436725

00:45:28.400 --> 00:45:31.680 individual physicians in the Congo,

NOTE Confidence: 0.8750436725

00:45:31.680 --> 00:45:32.236 Ghana,

NOTE Confidence: 0.8750436725

00:45:32.236 --> 00:45:35.016 Pakistan and Mali to establish

NOTE Confidence: 0.8750436725

00:45:35.016 --> 00:45:37.240 undiagnosed disease programs there.

NOTE Confidence: 0.8750436725

00:45:37.240 --> 00:45:40.219 And so the UD and I and the Willem

NOTE Confidence: 0.8750436725

00:45:40.219 --> 00:45:41.960 Foundation can provide resources

NOTE Confidence: 0.8750436725

00:45:41.960 --> 00:45:44.040 in terms of collaborations,

NOTE Confidence: 0.8750436725

00:45:44.040 --> 00:45:47.200 access to sequencing, some teaching.

NOTE Confidence: 0.8750436725

00:45:47.200 --> 00:45:49.195 In other words, people coming over to,

NOTE Confidence: 0.8750436725

00:45:49.200 --> 00:45:50.164 for example,

NOTE Confidence: 0.8750436725

00:45:50.164 --> 00:45:53.538 United States and Olaf Beaudemar's lab at

NOTE Confidence: 0.8750436725

00:45:53.538 --> 00:45:57.072 Harvard and some financial support that,

NOTE Confidence: 0.8750436725

00:45:57.072 --> 00:45:58.640 for example,

NOTE Confidence: 0.8750436725

00:45:58.640 --> 00:46:01.088 came to the Wilhelm Foundation from

NOTE Confidence: 0.8750436725

00:46:01.088 --> 00:46:03.115 the Chan Zuckerberg Initiative and

NOTE Confidence: 0.8750436725

00:46:03.115 --> 00:46:05.113 is being funneled them to these

NOTE Confidence: 0.8750436725

00:46:05.113 --> 00:46:06.800 champions in other countries.

NOTE Confidence: 0.933359871

00:46:09.520 --> 00:46:10.624 Yeah, this describes it.

NOTE Confidence: 0.933359871

00:46:10.624 --> 00:46:13.690 And this is one of the beautiful young

NOTE Confidence: 0.933359871

00:46:13.690 --> 00:46:17.920 patients in one of those countries.

NOTE Confidence: 0.933359871

00:46:17.920 --> 00:46:21.971 So I saw this leave you with the

NOTE Confidence: 0.933359871

00:46:21.971 --> 00:46:23.477 fact that there are many ways

NOTE Confidence: 0.933359871

00:46:23.477 --> 00:46:25.040 that we could work together.

NOTE Confidence: 0.933359871

00:46:25.040 --> 00:46:28.346 And I think you know there are referral

NOTE Confidence: 0.933359871

00:46:28.346 --> 00:46:29.876 of patients if you're interested,

NOTE Confidence: 0.933359871

00:46:29.880 --> 00:46:32.679 but you know we do have plenty of patients.

NOTE Confidence: 0.933359871

00:46:32.680 --> 00:46:36.226 But for example we have 1600 patients

NOTE Confidence: 0.933359871

00:46:36.226 --> 00:46:37.984 that we've seen and probably about

NOTE Confidence: 0.933359871

00:46:37.984 --> 00:46:39.957 800 of them have not been solved

NOTE Confidence: 0.933359871

00:46:39.960 --> 00:46:43.144 and we have genetics on them and

NOTE Confidence: 0.933359871

00:46:43.144 --> 00:46:45.040 really good phenotyping on them and

NOTE Confidence: 0.933359871

00:46:45.102 --> 00:46:47.076 we have fiberglass on most of them.

NOTE Confidence: 0.933359871

00:46:47.080 --> 00:46:49.753 So if you had a favorite gene and maybe

NOTE Confidence: 0.933359871

00:46:49.753 --> 00:46:52.330 there was a variance in that favorite

NOTE Confidence: 0.933359871

00:46:52.330 --> 00:46:55.000 gene that was associated with a phenotype,

NOTE Confidence: 0.933359871

00:46:55.000 --> 00:46:57.415 but it was only one patient and

NOTE Confidence: 0.933359871

00:46:57.415 --> 00:46:59.812 you didn't know if this variant and

NOTE Confidence: 0.933359871

00:46:59.812 --> 00:47:02.514 this gene was causal to the disease.

NOTE Confidence: 0.933359871

00:47:02.520 --> 00:47:04.293 You can tell me what the gene is and

NOTE Confidence: 0.933359871

00:47:04.293 --> 00:47:06.053 I'll tell you if we have a patient

NOTE Confidence: 0.933359871

00:47:06.053 --> 00:47:07.619 in our database that has a variance

NOTE Confidence: 0.933359871

00:47:07.619 --> 00:47:09.488 in that gene and then you can decide

NOTE Confidence: 0.933359871

00:47:09.488 --> 00:47:11.762 what you want to do with that Also.

NOTE Confidence: 0.933359871

00:47:11.762 --> 00:47:13.454 I think maybe I've already provided

NOTE Confidence: 0.933359871

00:47:13.454 --> 00:47:15.320 A protocol and consent and manual

NOTE Confidence: 0.933359871

00:47:15.320 --> 00:47:16.280 of operations here,

NOTE Confidence: 0.933359871

00:47:16.280 --> 00:47:18.096 but that's certainly available.

NOTE Confidence: 0.933359871

00:47:18.096 --> 00:47:21.186 I think our goal and maybe the

NOTE Confidence: 0.933359871

00:47:21.186 --> 00:47:24.496 goal of all of the physicians is to

NOTE Confidence: 0.933359871

00:47:24.496 --> 00:47:28.624 lend a helping hand and these are

NOTE Confidence: 0.933359871

00:47:28.624 --> 00:47:32.840 particularly needy group because

NOTE Confidence: 0.933359871

00:47:32.840 --> 00:47:34.358 not only isn't there a treatment,

NOTE Confidence: 0.933359871

00:47:34.360 --> 00:47:36.811 but there isn't a diagnosis and

NOTE Confidence: 0.933359871

00:47:36.811 --> 00:47:38.866 maybe especially there isn't even

NOTE Confidence: 0.933359871

00:47:38.866 --> 00:47:41.355 a community for them because they

NOTE Confidence: 0.933359871

00:47:41.355 --> 00:47:43.280 can't say what they have.

NOTE Confidence: 0.933359871

00:47:43.280 --> 00:47:44.318 So thank you for your attention.

NOTE Confidence: 0.2886124

00:47:59.720 --> 00:47:59.840 It's

NOTE Confidence: 0.622168525

00:48:02.440 --> 00:48:04.680 beautiful talk, beautiful stories.

NOTE Confidence: 0.622168525

00:48:04.680 --> 00:48:07.760 The story that is the most amazing

NOTE Confidence: 0.622168525

00:48:07.760 --> 00:48:09.386 is the story of the centre.

NOTE Confidence: 0.622168525

00:48:09.386 --> 00:48:13.448 In your story I had a question

NOTE Confidence: 0.622168525

00:48:13.448 --> 00:48:16.320 related to the tubulopathy that

NOTE Confidence: 0.746073094285714

00:48:16.600 --> 00:48:18.560 caused the Rick. It's not the Nigerian

NOTE Confidence: 0.7853329625

00:48:18.560 --> 00:48:20.080 one, but the tubular

NOTE Confidence: 0.7853329625

00:48:20.080 --> 00:48:23.560 mutation, and you describe

NOTE Confidence: 0.568649236666667

00:48:23.560 --> 00:48:26.959 the Fanconi syndromes.

NOTE Confidence: 0.568649236666667

00:48:26.960 --> 00:48:28.198 You couldn't tell whether it was

NOTE Confidence: 0.568649236666667

00:48:28.198 --> 00:48:30.120 isolated to phosphorus or other solutes

NOTE Confidence: 0.568649236666667

00:48:30.120 --> 00:48:33.960 were part of that phenotype as being.

NOTE Confidence: 0.18224706

00:48:36.120 --> 00:48:40.130 And I wondered if this might tell

NOTE Confidence: 0.18224706

00:48:40.130 --> 00:48:42.200 us if that protein has a specific

NOTE Confidence: 0.648465566666667

00:48:42.920 --> 00:48:44.759 role in intracellular

NOTE Confidence: 0.830780935

00:48:44.760 --> 00:48:47.320 trafficking of phosphate transporters

NOTE Confidence: 0.830780935

00:48:47.320 --> 00:48:50.080 versus other solute transporters.

NOTE Confidence: 0.692209108333333

00:48:51.160 --> 00:48:52.678 No, you you, you're you're right.

NOTE Confidence: 0.7140661325

00:48:52.760 --> 00:48:55.680 And I failed to mention that the pancoli

NOTE Confidence: 0.7140661325

00:48:55.680 --> 00:48:57.960 syndrome was, I would say isolated.

NOTE Confidence: 0.7140661325

00:48:57.960 --> 00:49:00.600 In other words, she did not have, you know,

NOTE Confidence: 0.5491280625

00:49:00.640 --> 00:49:02.960 Asturia or small molecular

NOTE Confidence: 0.651908989230769

00:49:02.960 --> 00:49:05.150 reporter. Yeah, she said that's why

NOTE Confidence: 0.651908989230769

00:49:05.150 --> 00:49:07.479 the hypothesis was that it was really

NOTE Confidence: 0.651908989230769

00:49:07.480 --> 00:49:10.400 the SLC or yeah, whatever it was. But I

NOTE Confidence: 0.868227968333333

00:49:10.400 --> 00:49:14.360 I think you're you're right that

NOTE Confidence: 0.868227968333333

00:49:14.360 --> 00:49:16.999 the microtubules made the important

NOTE Confidence: 0.869517426

00:49:17.560 --> 00:49:22.380 in other cells of the tubules of the

NOTE Confidence: 0.869517426

00:49:22.380 --> 00:49:26.160 kidney for transport of transporters,

NOTE Confidence: 0.869517426

00:49:26.160 --> 00:49:28.380 for movement of transporters to the membrane.

NOTE Confidence: 0.869517426

00:49:28.380 --> 00:49:32.920 And that has not been investigated in in fact

NOTE Confidence: 0.651142104285714

00:49:32.920 --> 00:49:34.800 the scene that I showed you was hypothetical.

NOTE Confidence: 0.651142104285714

00:49:34.800 --> 00:49:37.360 So we haven't actually demonstrated that that

NOTE Confidence: 0.651142104285714

00:49:37.360 --> 00:49:39.398 transporter didn't get there and that that

NOTE Confidence: 0.566783206

00:49:39.400 --> 00:49:42.320 was the cause that's this bottom

NOTE Confidence: 0.6676786

00:49:45.960 --> 00:49:47.848 doctor. Thank you for the

NOTE Confidence: 0.6676786

00:49:47.848 --> 00:49:50.360 inspirational background.

NOTE Confidence: 0.6676786

00:49:50.360 --> 00:49:52.360 The question I had was about your

NOTE Confidence: 0.6676786

00:49:52.360 --> 00:49:54.360 story about phenotype expansion.

NOTE Confidence: 0.61756817

00:49:55.160 --> 00:49:59.240 And as clinicians and diagnosticians,

NOTE Confidence: 0.719514035714286

00:49:59.560 --> 00:50:02.542 we often come across symbol gene

NOTE Confidence: 0.719514035714286

00:50:02.542 --> 00:50:04.740 disorder and it is actually able to

NOTE Confidence: 0.719514035714286

00:50:04.740 --> 00:50:07.680 talk about phenotype attention whenever

NOTE Confidence: 0.719514035714286

00:50:07.680 --> 00:50:09.972 there are any news from stations.

NOTE Confidence: 0.719514035714286

00:50:09.972 --> 00:50:12.680 So in this group of patients,

NOTE Confidence: 0.719514035714286

00:50:12.680 --> 00:50:15.360 are they two genetic diseases and

NOTE Confidence: 0.719514035714286

00:50:15.360 --> 00:50:17.946 some work by Jennifer Posey have

NOTE Confidence: 0.719514035714286

00:50:17.946 --> 00:50:21.171 shown that up to 5% may be higher.

NOTE Confidence: 0.719514035714286

00:50:21.171 --> 00:50:24.597 Individuals have two diseases coming together

NOTE Confidence: 0.3595053625

00:50:24.960 --> 00:50:27.480 at bending or penotrive.

NOTE Confidence: 0.3595053625

00:50:27.480 --> 00:50:29.936 So my question to you is in the

NOTE Confidence: 0.3595053625

00:50:29.936 --> 00:50:32.336 undiagnosed disease program, are you

NOTE Confidence: 0.3595053625

00:50:32.336 --> 00:50:34.560 recognizing that history? The answer

NOTE Confidence: 0.75406752

00:50:34.560 --> 00:50:36.808 is yes. We look for it.

NOTE Confidence: 0.75406752

00:50:36.808 --> 00:50:38.534 I I think that the expansion of

NOTE Confidence: 0.75406752

00:50:38.534 --> 00:50:40.024 phenotype was a little different

NOTE Confidence: 0.75406752

00:50:40.024 --> 00:50:41.320 because we could explain

NOTE Confidence: 0.7341931

00:50:41.640 --> 00:50:44.200 you know the other phenotypes findings,

NOTE Confidence: 0.912321268571429

00:50:44.520 --> 00:50:47.439 but we have a number of cases

NOTE Confidence: 0.912321268571429

00:50:47.440 --> 00:50:49.400 that we think that there's another

NOTE Confidence: 0.912321268571429

00:50:49.400 --> 00:50:51.800 gene involved and it's not just

NOTE Confidence: 0.912321268571429

00:50:51.800 --> 00:50:53.640 that it's a modifying gene,

NOTE Confidence: 0.912321268571429

00:50:53.640 --> 00:50:57.360 it's another monogenic disease

NOTE Confidence: 0.912321268571429

00:50:57.360 --> 00:50:59.080 that we haven't figured out.

NOTE Confidence: 0.912321268571429

00:50:59.080 --> 00:51:00.816 But when you have two of them,

NOTE Confidence: 0.912321268571429

00:51:00.816 --> 00:51:02.288 it's really and and and

NOTE Confidence: 0.912321268571429

00:51:02.288 --> 00:51:03.290 when they're both new,

NOTE Confidence: 0.912321268571429

00:51:03.290 --> 00:51:06.144 it's really difficult to distinguish the

NOTE Confidence: 0.912321268571429

00:51:06.144 --> 00:51:07.968 which of the phenotypes is associated

NOTE Confidence: 0.912321268571429

00:51:07.968 --> 00:51:09.776 with one variant and which might be

NOTE Confidence: 0.912321268571429

00:51:09.776 --> 00:51:11.878 associated with another variant.

NOTE Confidence: 0.912321268571429

00:51:11.880 --> 00:51:13.460 And I I guess I was talking to

NOTE Confidence: 0.912321268571429

00:51:13.460 --> 00:51:15.000 some of the people to hear that

NOTE Confidence: 0.935563434285714

00:51:17.040 --> 00:51:19.746 the pursuit of those really difficult

NOTE Confidence: 0.935563434285714

00:51:19.746 --> 00:51:22.340 cases takes this much effort and

NOTE Confidence: 0.935563434285714

00:51:22.340 --> 00:51:24.520 the pursuit of a new case that

NOTE Confidence: 0.935563434285714

00:51:24.520 --> 00:51:26.600 we see takes this much effort to

NOTE Confidence: 0.92969729375

00:51:26.600 --> 00:51:30.040 get solution. Where should we spend our money

NOTE Confidence: 0.937945505

00:51:30.160 --> 00:51:32.398 and our resources and our time?

NOTE Confidence: 0.937945505

00:51:32.400 --> 00:51:35.300 So in a way we have to go for those

NOTE Confidence: 0.937945505

00:51:35.300 --> 00:51:36.879 really unusual cases that do match

NOTE Confidence: 0.7159652375

00:51:36.880 --> 00:51:42.580 it that could be digenic and that

NOTE Confidence: 0.7159652375

00:51:42.580 --> 00:51:45.240 will give us a good reputation and

NOTE Confidence: 0.7159652375

00:51:45.240 --> 00:51:48.024 a big paper and stuff like that.

NOTE Confidence: 0.7159652375

00:51:48.024 --> 00:51:50.640 But in that, in the time that we spend

NOTE Confidence: 0.89826650125

00:51:50.640 --> 00:51:54.120 for that, we could see three new cases and

NOTE Confidence: 0.89826650125

00:51:54.120 --> 00:51:56.880 diagnose two of them or whatever, you know.

NOTE Confidence: 0.89826650125

00:51:56.880 --> 00:51:59.100 So really it's a prioritization issue,

NOTE Confidence: 0.89826650125

00:51:59.100 --> 00:52:00.864 but the answer is yes.

NOTE Confidence: 0.89826650125

00:52:00.864 --> 00:52:03.120 We think that we see number

NOTE Confidence: 0.89826650125

00:52:03.120 --> 00:52:06.080 of diagenic disorders.

NOTE Confidence: 0.89826650125

00:52:06.080 --> 00:52:09.160 I remember when I was working on cystinosis,

NOTE Confidence: 0.89826650125

00:52:09.160 --> 00:52:12.080 we had a young man with cystinosis

NOTE Confidence: 0.89826650125

00:52:12.080 --> 00:52:14.316 and when he ran the first base playing

NOTE Confidence: 0.89826650125

00:52:14.320 --> 00:52:17.560 ball as an adolescent, his fever.

NOTE Confidence: 0.89826650125

00:52:17.560 --> 00:52:20.479 Turns out he also had the braces,

NOTE Confidence: 0.89826650125

00:52:20.480 --> 00:52:24.279 and we actually published that as an example.

NOTE Confidence: 0.89826650125

00:52:24.280 --> 00:52:26.398 But you know,

NOTE Confidence: 0.89826650125

00:52:26.400 --> 00:52:28.194 just because you have water energy

NOTE Confidence: 0.89826650125

00:52:28.194 --> 00:52:29.998 doesn't need not to get it on.

NOTE Confidence: 0.4638641

00:52:49.840 --> 00:52:50.760 OK, let's just

NOTE Confidence: 0.488144696666667

00:52:52.960 --> 00:52:53.840 first she says thank you.

NOTE Confidence: 0.33304226

00:52:57.520 --> 00:52:59.252 My question is of hundreds

NOTE Confidence: 0.33304226

00:52:59.252 --> 00:53:02.400 of candidates Snips and then

NOTE Confidence: 0.326437836666667

00:53:02.400 --> 00:53:04.080 Glenbar and Polygon,

NOTE Confidence: 0.326437836666667

00:53:04.080 --> 00:53:06.136 DAD later than that has been

NOTE Confidence: 0.326437836666667

00:53:06.136 --> 00:53:08.440 invariant significance.

NOTE Confidence: 0.326437836666667

00:53:08.440 --> 00:53:09.478 How do you think of all

NOTE Confidence: 0.326437836666667

00:53:09.480 --> 00:53:11.960 topical pathogenic variants?

NOTE Confidence: 0.42417485

00:53:14.840 --> 00:53:18.120 Well, you can. You can

NOTE Confidence: 0.7779566

00:53:20.120 --> 00:53:20.880 see that

NOTE Confidence: 0.889967443333333

00:53:23.640 --> 00:53:26.280 one thing is the punitive

NOTE Confidence: 0.889967443333333

00:53:26.280 --> 00:53:27.880 inheritance pattern.

NOTE Confidence: 0.889967443333333

00:53:27.880 --> 00:53:32.160 So you pretty much can't single

NOTE Confidence: 0.889967443333333

00:53:32.160 --> 00:53:33.400 out those paths with the periods.

NOTE Confidence: 0.889967443333333

00:53:33.400 --> 00:53:35.040 If you just do a single Excel,

NOTE Confidence: 0.889967443333333

00:53:35.040 --> 00:53:36.678 you don't have the first thing.

NOTE Confidence: 0.889967443333333

00:53:36.680 --> 00:53:38.360 So if you have the parents,

NOTE Confidence: 0.889967443333333

00:53:38.360 --> 00:53:42.600 you can tell if it's inherited and if

NOTE Confidence: 0.889967443333333

00:53:42.600 --> 00:53:45.438 the IT segregates with the disease.

NOTE Confidence: 0.889967443333333

00:53:45.440 --> 00:53:49.157 So extremely important to have the parents,

NOTE Confidence: 0.889967443333333

00:53:49.160 --> 00:53:51.575 the truth, the trios are critical and

NOTE Confidence: 0.889967443333333

00:53:51.575 --> 00:53:54.590 then a quartet is helpful as well.

NOTE Confidence: 0.889967443333333

00:53:54.590 --> 00:53:55.728 So another sibling that's

NOTE Confidence: 0.889967443333333

00:53:55.728 --> 00:53:56.560 either affected or not

NOTE Confidence: 0.64667496

00:53:56.560 --> 00:53:58.876 affected and all that that's also

NOTE Confidence: 0.64667496

00:53:58.880 --> 00:54:00.760 beneficial, not as beneficial

NOTE Confidence: 0.805149734

00:54:00.760 --> 00:54:04.192 as having the parents alone. And then

NOTE Confidence: 0.805149734

00:54:04.192 --> 00:54:05.760 to have a fifth member of the family

NOTE Confidence: 0.9072351075

00:54:05.760 --> 00:54:07.000 isn't quite so important.

NOTE Confidence: 0.48911887625

00:54:07.960 --> 00:54:10.540 It's the quartet and the trio

NOTE Confidence: 0.48911887625

00:54:10.540 --> 00:54:13.050 says for, But the the point is

NOTE Confidence: 0.48911887625

00:54:13.050 --> 00:54:14.638 that the inheritance pattern

NOTE Confidence: 0.90304823

00:54:14.640 --> 00:54:17.517 and knowing who is affected by doing

NOTE Confidence: 0.90304823

00:54:17.520 --> 00:54:19.840 extensive phenotyping will help

NOTE Confidence: 0.949716771428571

00:54:19.840 --> 00:54:22.318 you to eliminate a huge number of

NOTE Confidence: 0.869809204

00:54:22.320 --> 00:54:24.920 the variants that have not

NOTE Confidence: 0.869809204

00:54:24.920 --> 00:54:27.266 already been eliminated by being

NOTE Confidence: 0.869809204

00:54:27.266 --> 00:54:29.200 associated with a benign phenotype.

NOTE Confidence: 0.875502551111111

00:54:31.440 --> 00:54:33.712 But a lot of times we'll end up

NOTE Confidence: 0.875502551111111

00:54:33.712 --> 00:54:36.310 with 510 or 20 variants that are

NOTE Confidence: 0.875502551111111

00:54:36.310 --> 00:54:37.920 candidates for causing the disease

NOTE Confidence: 0.875502551111111

00:54:37.920 --> 00:54:41.320 and then depending upon how specific

NOTE Confidence: 0.779405462307692

00:54:41.320 --> 00:54:44.358 the disease is determines how much we'll

NOTE Confidence: 0.779405462307692

00:54:44.358 --> 00:54:47.519 invest in the gene function studies.

NOTE Confidence: 0.779405462307692

00:54:47.520 --> 00:54:49.200 You know, because if there's now

NOTE Confidence: 0.779405462307692

00:54:49.200 --> 00:54:50.959 specificity in the phenotype,

NOTE Confidence: 0.86239652

00:54:51.320 --> 00:54:52.390 we're not going to spend

NOTE Confidence: 0.86239652

00:54:52.390 --> 00:54:53.600 a lot of time looking at

NOTE Confidence: 0.64192848

00:54:53.760 --> 00:54:58.120 such a very causing dysfunction.

NOTE Confidence: 0.48854129

00:55:03.440 --> 00:55:03.840 Anything else

NOTE Confidence: 0.183620285

00:55:24.880 --> 00:55:25.760 and diagnose?

NOTE Confidence: 0.44527761

00:55:28.760 --> 00:55:30.440 Thanks for popping

NOTE Confidence: 0.5429746

00:55:43.240 --> 00:55:43.320 up.