

WEBVTT

NOTE duration:"00:16:26.2210000"

NOTE language:en-us

NOTE Confidence: 0.8506553

00:00:00.000 --> 00:00:01.146 Good afternoon everyone.

NOTE Confidence: 0.8506553

00:00:01.146 --> 00:00:04.844 My name is Nicole Lake and I'm a postdoctoral

NOTE Confidence: 0.8506553

00:00:04.844 --> 00:00:07.706 associate in the Department of Genetics.

NOTE Confidence: 0.8506553

00:00:07.710 --> 00:00:10.244 It's my great pleasure to now introduce

NOTE Confidence: 0.8506553

00:00:10.244 --> 00:00:12.195 Doctor Martina Brueckner Doctor Bruckner

NOTE Confidence: 0.8506553

00:00:12.195 --> 00:00:14.205 received her undergraduate and medical

NOTE Confidence: 0.8506553

00:00:14.205 --> 00:00:16.770 degrees from the University of Virginia,

NOTE Confidence: 0.8506553

00:00:16.770 --> 00:00:18.900 then trained in Pediatrics at the

NOTE Confidence: 0.8506553

00:00:18.900 --> 00:00:21.260 University of Pittsburgh and completed her

NOTE Confidence: 0.8506553

00:00:21.260 --> 00:00:23.465 pediatric cardiology fellowship at Yale.

NOTE Confidence: 0.8506553

00:00:23.470 --> 00:00:25.440 She has been on the

NOTE Confidence: 0.8506553

00:00:25.440 --> 00:00:27.410 faculty at Yale since 1991,

NOTE Confidence: 0.8506553

00:00:27.410 --> 00:00:29.014 where she provided clinical,

NOTE Confidence: 0.8506553

00:00:29.014 --> 00:00:31.019 pediatric cardiology care and founded

NOTE Confidence: 0.8506553

00:00:31.019 --> 00:00:33.030 the Yale Pediatric Cardi Attic.

NOTE Confidence: 0.8506553

00:00:33.030 --> 00:00:34.449 Cardiac genetics clinic.

NOTE Confidence: 0.8506553

00:00:34.449 --> 00:00:36.814 Her laboratory now focuses on

NOTE Confidence: 0.8506553

00:00:36.814 --> 00:00:39.231 the molecular and genetic causes

NOTE Confidence: 0.8506553

00:00:39.231 --> 00:00:41.099 of congenital heart disease,

NOTE Confidence: 0.8506553

00:00:41.100 --> 00:00:43.644 with a special focus on the role of

NOTE Confidence: 0.8506553

00:00:43.644 --> 00:00:46.530 cilia in heart development and disease.

NOTE Confidence: 0.8506553

00:00:46.530 --> 00:00:48.460 She has LED Yale's participation

NOTE Confidence: 0.8506553

00:00:48.460 --> 00:00:50.390 in the pediatric Cardiac Genomics

NOTE Confidence: 0.8506553

00:00:50.455 --> 00:00:52.735 Consortium since its inception in 2009.

NOTE Confidence: 0.8506553

00:00:52.740 --> 00:00:55.850 The zoom floor is now yours, Doctor Bruckner.

NOTE Confidence: 0.78951025

00:00:56.600 --> 00:01:01.190 Thank you, let me share screen.

NOTE Confidence: 0.21786205

00:01:09.520 --> 00:01:12.921 Wait? There we go.

NOTE Confidence: 0.21786205

00:01:12.921 --> 00:01:14.956 Is that visible for everybody?

NOTE Confidence: 0.8755123

00:01:17.490 --> 00:01:20.418 I believe so yes. OK, so I'm going

NOTE Confidence: 0.8755123

00:01:20.418 --> 00:01:22.440 to be talking about the genetic
NOTE Confidence: 0.8755123

00:01:22.518 --> 00:01:24.978 causes of congenital heart disease,
NOTE Confidence: 0.8755123

00:01:24.980 --> 00:01:27.344 which is and I don't have
NOTE Confidence: 0.8755123

00:01:27.344 --> 00:01:28.920 any conflicts of interest.
NOTE Confidence: 0.8755123

00:01:28.920 --> 00:01:30.492 So congenital heart disease
NOTE Confidence: 0.8755123

00:01:30.492 --> 00:01:32.457 is quite a common problem.
NOTE Confidence: 0.8755123

00:01:32.460 --> 00:01:35.604 It affects one in 100 life born infants.
NOTE Confidence: 0.8755123

00:01:35.610 --> 00:01:38.368 90% of our patients survived to adulthood,
NOTE Confidence: 0.8755123

00:01:38.370 --> 00:01:41.156 which is definitely a change over the
NOTE Confidence: 0.8755123

00:01:41.156 --> 00:01:43.889 time that I've been in this field,
NOTE Confidence: 0.8755123

00:01:43.890 --> 00:01:45.678 but many suffer comorbidities,
NOTE Confidence: 0.8755123

00:01:45.678 --> 00:01:46.572 including neurodevelopmental
NOTE Confidence: 0.8755123

00:01:46.572 --> 00:01:47.913 and respiratory problems.
NOTE Confidence: 0.8755123

00:01:47.920 --> 00:01:50.380 What we've come to believe is
NOTE Confidence: 0.8755123

00:01:50.380 --> 00:01:52.942 that about 90% of patients with
NOTE Confidence: 0.8755123

00:01:52.942 --> 00:01:55.162 congenital heart disease have a

NOTE Confidence: 0.8755123

00:01:55.162 --> 00:01:56.970 significant genetic contribution.

NOTE Confidence: 0.8755123

00:01:56.970 --> 00:01:58.700 And unlike in the past,

NOTE Confidence: 0.8755123

00:01:58.700 --> 00:02:01.805 this is no longer an itch kind of disease.

NOTE Confidence: 0.8755123

00:02:01.810 --> 00:02:04.578 If you look at these statistics from 2010,

NOTE Confidence: 0.8755123

00:02:04.580 --> 00:02:06.135 there are two point 4,000,000

NOTE Confidence: 0.8755123

00:02:06.135 --> 00:02:08.153 people in the United States living

NOTE Confidence: 0.8755123

00:02:08.153 --> 00:02:09.769 with congenital heart disease.

NOTE Confidence: 0.8755123

00:02:09.770 --> 00:02:11.500 1,000,000 are under 18 years,

NOTE Confidence: 0.8755123

00:02:11.500 --> 00:02:13.576 1.4 million are over 18 years,

NOTE Confidence: 0.8755123

00:02:13.580 --> 00:02:14.645 and since 210,

NOTE Confidence: 0.8755123

00:02:14.645 --> 00:02:16.420 the proportion of those that

NOTE Confidence: 0.8755123

00:02:16.420 --> 00:02:19.554 are in the over 18 years of age

NOTE Confidence: 0.8755123

00:02:19.554 --> 00:02:21.118 range has grown significantly.

NOTE Confidence: 0.8755123

00:02:21.120 --> 00:02:21.538 Also,

NOTE Confidence: 0.8755123

00:02:21.538 --> 00:02:23.628 looking at the population disease

NOTE Confidence: 0.8755123

00:02:23.628 --> 00:02:25.300 statistics in other countries,
NOTE Confidence: 0.8755123

00:02:25.300 --> 00:02:28.317 there are in Canada 257 thousand people
NOTE Confidence: 0.8755123

00:02:28.317 --> 00:02:30.483 living with congenital heart disease
NOTE Confidence: 0.8755123

00:02:30.483 --> 00:02:32.865 as compared to for instance 71,000
NOTE Confidence: 0.8755123

00:02:32.865 --> 00:02:35.750 with HIV or 4000 with cystic fibrosis.
NOTE Confidence: 0.8755123

00:02:35.750 --> 00:02:38.870 So this is a common problem that touches
NOTE Confidence: 0.8755123

00:02:38.870 --> 00:02:42.016 quite many aspects of the medical system.
NOTE Confidence: 0.8755123

00:02:42.020 --> 00:02:44.105 The outcome in congenital heart
NOTE Confidence: 0.8755123

00:02:44.105 --> 00:02:45.773 disease is incredibly variable,
NOTE Confidence: 0.8755123

00:02:45.780 --> 00:02:48.734 so a very common type of congenital
NOTE Confidence: 0.8755123

00:02:48.734 --> 00:02:52.007 heart disease tetralogy of fellow can be
NOTE Confidence: 0.8755123

00:02:52.007 --> 00:02:53.939 surgically repaired very affectively.
NOTE Confidence: 0.8755123

00:02:53.940 --> 00:02:55.056 Post operatively him,
NOTE Confidence: 0.8755123

00:02:55.056 --> 00:02:56.916 the children will quite compromised.
NOTE Confidence: 0.8755123

00:02:56.920 --> 00:02:59.688 However many of them grow up and are
NOTE Confidence: 0.8755123

00:02:59.688 --> 00:03:02.332 quite fine as seen here by Shaun

NOTE Confidence: 0.8755123

00:03:02.332 --> 00:03:04.730 White winning an Olympic gold medal.

NOTE Confidence: 0.8755123

00:03:04.730 --> 00:03:06.478 He is status post.

NOTE Confidence: 0.8755123

00:03:06.478 --> 00:03:09.100 I believe three tetralogy surgeries however.

NOTE Confidence: 0.8755123

00:03:09.100 --> 00:03:11.795 If you look at the serious adverse

NOTE Confidence: 0.8755123

00:03:11.795 --> 00:03:14.770 events in this population as a whole,

NOTE Confidence: 0.8755123

00:03:14.770 --> 00:03:16.390 they are quite significant,

NOTE Confidence: 0.8755123

00:03:16.390 --> 00:03:18.820 and by the age of 30,

NOTE Confidence: 0.8755123

00:03:18.820 --> 00:03:21.641 about 910% will have suffered a serious

NOTE Confidence: 0.8755123

00:03:21.641 --> 00:03:23.712 adverse event and somewhere between

NOTE Confidence: 0.8755123

00:03:23.712 --> 00:03:27.600 15 and 20% a significant adverse event.

NOTE Confidence: 0.8755123

00:03:27.600 --> 00:03:29.560 So the question we have is whether

NOTE Confidence: 0.8755123

00:03:29.560 --> 00:03:31.228 genetics can lead to personalized

NOTE Confidence: 0.8755123

00:03:31.228 --> 00:03:33.163 treatment of congenital heart disease

NOTE Confidence: 0.8755123

00:03:33.163 --> 00:03:35.140 and the associated comorbidities,

NOTE Confidence: 0.8755123

00:03:35.140 --> 00:03:36.934 and so a national consortium was

NOTE Confidence: 0.8755123

00:03:36.934 --> 00:03:39.121 formed in 2009 called the Pediatric
NOTE Confidence: 0.8755123

00:03:39.121 --> 00:03:40.516 Cardiac Genomics Consortium,
NOTE Confidence: 0.8755123

00:03:40.520 --> 00:03:43.160 and Yale was one of the founders of
NOTE Confidence: 0.8755123

00:03:43.160 --> 00:03:45.908 that group when it was first developed.
NOTE Confidence: 0.8755123

00:03:45.910 --> 00:03:48.058 Here are the current set of
NOTE Confidence: 0.8755123

00:03:48.058 --> 00:03:48.774 principle investigators.
NOTE Confidence: 0.8755123

00:03:48.780 --> 00:03:52.284 The main thing that this group has done.
NOTE Confidence: 0.8755123

00:03:52.290 --> 00:03:54.858 And we wanted to discover all the genes
NOTE Confidence: 0.8755123

00:03:54.858 --> 00:03:57.170 that cause congenital heart disease,
NOTE Confidence: 0.8755123

00:03:57.170 --> 00:03:58.670 identify the mutations responsible
NOTE Confidence: 0.8755123

00:03:58.670 --> 00:04:00.170 for congenital heart disease,
NOTE Confidence: 0.8755123

00:04:00.170 --> 00:04:04.330 and then link those findings to the outcome.
NOTE Confidence: 0.8755123

00:04:04.330 --> 00:04:07.390 What we've done so far as we for Crew did
NOTE Confidence: 0.8755123

00:04:07.465 --> 00:04:10.597 14,000 patients and over 14,000 relatives.
NOTE Confidence: 0.8755123

00:04:10.600 --> 00:04:12.560 This is the largest congenital
NOTE Confidence: 0.8755123

00:04:12.560 --> 00:04:13.736 disease cohort anywhere.

NOTE Confidence: 0.8755123

00:04:13.740 --> 00:04:16.477 The cardiac phenotyping was done by Echo.

NOTE Confidence: 0.8755123

00:04:16.480 --> 00:04:17.656 There's more superficial

NOTE Confidence: 0.8755123

00:04:17.656 --> 00:04:18.440 extracardiac phenotyping.

NOTE Confidence: 0.8755123

00:04:18.440 --> 00:04:20.400 We developed a database called

NOTE Confidence: 0.8755123

00:04:20.400 --> 00:04:22.360 Heart Smart and Mind you,

NOTE Confidence: 0.8755123

00:04:22.360 --> 00:04:25.496 this database was developed in 2009 and 2010,

NOTE Confidence: 0.8755123

00:04:25.500 --> 00:04:27.810 so we're now realizing it is

NOTE Confidence: 0.8755123

00:04:27.810 --> 00:04:30.211 grossly outdated and we have work

NOTE Confidence: 0.8755123

00:04:30.211 --> 00:04:32.545 in progress to link the genomic.

NOTE Confidence: 0.8755123

00:04:32.550 --> 00:04:34.900 An electronic medical record data.

NOTE Confidence: 0.8755123

00:04:34.900 --> 00:04:36.909 Or yell came into this is that

NOTE Confidence: 0.8755123

00:04:36.909 --> 00:04:37.770 the El Center

NOTE Confidence: 0.8051783

00:04:37.835 --> 00:04:40.481 for Genome Analysis has been the sequencing

NOTE Confidence: 0.8051783

00:04:40.481 --> 00:04:43.508 Center for the program since its inception.

NOTE Confidence: 0.8051783

00:04:43.510 --> 00:04:45.735 A man they have sequenced

NOTE Confidence: 0.8051783

00:04:45.735 --> 00:04:47.515 4075 program parent trios.
NOTE Confidence: 0.8051783

00:04:47.520 --> 00:04:49.745 So that's about 13,000 exomes
NOTE Confidence: 0.8051783

00:04:49.745 --> 00:04:51.524 17125 Singleton probands. Answer.
NOTE Confidence: 0.8051783

00:04:51.524 --> 00:04:55.076 Currently in the process of doing many more,
NOTE Confidence: 0.8051783

00:04:55.080 --> 00:04:56.860 there's also whole genome
NOTE Confidence: 0.8051783

00:04:56.860 --> 00:04:57.750 sequencing available.
NOTE Confidence: 0.8051783

00:04:57.750 --> 00:05:00.814 And as I'll talk about later why SGA
NOTE Confidence: 0.8051783

00:05:00.814 --> 00:05:03.538 helped develop some targeted sequencing,
NOTE Confidence: 0.8051783

00:05:03.540 --> 00:05:06.030 that allowed us to expand our
NOTE Confidence: 0.8051783

00:05:06.030 --> 00:05:08.430 cohort size were also banking,
NOTE Confidence: 0.8051783

00:05:08.430 --> 00:05:09.942 cardiac surgical tissue.
NOTE Confidence: 0.8051783

00:05:09.942 --> 00:05:12.966 So the main findings from the
NOTE Confidence: 0.8051783

00:05:12.966 --> 00:05:15.908 1st 10 years of this effort is.
NOTE Confidence: 0.8051783

00:05:15.910 --> 00:05:18.689 There are really 22 major sort of
NOTE Confidence: 0.8051783

00:05:18.689 --> 00:05:20.378 biological mechanisms that might
NOTE Confidence: 0.8051783

00:05:20.378 --> 00:05:22.528 link to congenital heart disease.

NOTE Confidence: 0.8051783

00:05:22.530 --> 00:05:25.020 Recessive mutations in the cilia genes.

NOTE Confidence: 0.8051783

00:05:25.020 --> 00:05:27.504 These are patients that might also

NOTE Confidence: 0.8051783

00:05:27.504 --> 00:05:29.160 have some respiratory compromise.

NOTE Confidence: 0.8051783

00:05:29.160 --> 00:05:30.884 Dominant mutations in chromatin

NOTE Confidence: 0.8051783

00:05:30.884 --> 00:05:32.608 modifier genes that associate

NOTE Confidence: 0.8051783

00:05:32.608 --> 00:05:34.290 specific subtypes of congenital

NOTE Confidence: 0.8051783

00:05:34.290 --> 00:05:36.200 heart disease and most importantly,

NOTE Confidence: 0.8051783

00:05:36.200 --> 00:05:37.870 these are mutations that really

NOTE Confidence: 0.8051783

00:05:37.870 --> 00:05:40.022 provide a biomarker that a patient

NOTE Confidence: 0.8051783

00:05:40.022 --> 00:05:42.962 is at very high risk for developing

NOTE Confidence: 0.8051783

00:05:42.962 --> 00:05:44.359 neurodevelopmental compromise and

NOTE Confidence: 0.8051783

00:05:44.359 --> 00:05:46.809 might benefit from more aggressive

NOTE Confidence: 0.8051783

00:05:46.809 --> 00:05:47.789 neurodevelopmental follow-up.

NOTE Confidence: 0.8542902

00:05:50.010 --> 00:05:52.060 The congenital heart disease genetics,

NOTE Confidence: 0.8542902

00:05:52.060 --> 00:05:53.560 however, is really incredibly

NOTE Confidence: 0.8542902

00:05:53.560 --> 00:05:54.685 complicated and characterized
NOTE Confidence: 0.8542902

00:05:54.685 --> 00:05:56.570 by vast genetic heterogeneity,
NOTE Confidence: 0.8542902

00:05:56.570 --> 00:05:59.030 so this is the sequencing data.
NOTE Confidence: 0.8542902

00:05:59.030 --> 00:06:01.490 Over the course of the project,
NOTE Confidence: 0.8542902

00:06:01.490 --> 00:06:05.220 we started with 362 trios at a time when we
NOTE Confidence: 0.8542902

00:06:05.310 --> 00:06:08.870 were told that that was a vast overreach,
NOTE Confidence: 0.8542902

00:06:08.870 --> 00:06:12.970 and we would never be able to pay for it.
NOTE Confidence: 0.8542902

00:06:12.970 --> 00:06:16.379 I believe a single exon at that
NOTE Confidence: 0.8542902

00:06:16.379 --> 00:06:19.110 time was somewhere around \$800.
NOTE Confidence: 0.8542902

00:06:19.110 --> 00:06:21.050 That we have now progressed,
NOTE Confidence: 0.8542902

00:06:21.050 --> 00:06:23.366 obviously to a much larger number,
NOTE Confidence: 0.8542902

00:06:23.370 --> 00:06:26.430 and you can see that the number of genes
NOTE Confidence: 0.8542902

00:06:26.430 --> 00:06:29.515 with significant IKA more than one damaging
NOTE Confidence: 0.8542902

00:06:29.515 --> 00:06:33.038 de Novo mutation has expanded from 2 to 95.
NOTE Confidence: 0.8542902

00:06:33.040 --> 00:06:36.136 However, when you take all the data together,
NOTE Confidence: 0.8542902

00:06:36.140 --> 00:06:38.800 we predict that at least 400 genes

NOTE Confidence: 0.8542902

00:06:38.800 --> 00:06:40.398 contribute to congenital heart

NOTE Confidence: 0.8542902

00:06:40.398 --> 00:06:42.720 disease by a denovo mechanism alone,

NOTE Confidence: 0.8542902

00:06:42.720 --> 00:06:45.976 and that's not counting all the genes and

NOTE Confidence: 0.8542902

00:06:45.976 --> 00:06:48.584 biological pathways that may be implicated

NOTE Confidence: 0.8542902

00:06:48.584 --> 00:06:50.734 as recessive or contributing genes.

NOTE Confidence: 0.8542902

00:06:50.740 --> 00:06:53.253 We think we need about 10,000 trios

NOTE Confidence: 0.8542902

00:06:53.253 --> 00:06:55.658 to identify 50% of the genes that

NOTE Confidence: 0.8542902

00:06:55.658 --> 00:06:56.986 cause congenital heart disease

NOTE Confidence: 0.8542902

00:06:56.986 --> 00:06:58.640 by de Novo mechanism.

NOTE Confidence: 0.8542902

00:06:58.640 --> 00:07:01.168 Probably 20 to 30,000 to begin to define

NOTE Confidence: 0.8542902

00:07:01.168 --> 00:07:02.950 the multigenic genetic mechanisms.

NOTE Confidence: 0.8542902

00:07:02.950 --> 00:07:05.694 So we're really now lost in that

NOTE Confidence: 0.8542902

00:07:05.694 --> 00:07:08.039 middle heavy digging part that IRA

NOTE Confidence: 0.8542902

00:07:08.039 --> 00:07:10.217 alluded to at the very beginning

NOTE Confidence: 0.8542902

00:07:10.217 --> 00:07:12.949 of this session of this symposium.

NOTE Confidence: 0.8542902

00:07:12.950 --> 00:07:15.128 And we probably need very large
NOTE Confidence: 0.8542902

00:07:15.128 --> 00:07:17.608 numbers to understand the genetics of
NOTE Confidence: 0.8542902

00:07:17.608 --> 00:07:19.998 specific congenital heart disease sub
NOTE Confidence: 0.8542902

00:07:19.998 --> 00:07:21.847 phenotypes because really congenital
NOTE Confidence: 0.8542902

00:07:21.847 --> 00:07:24.599 heart disease as a whole is just a
NOTE Confidence: 0.8542902

00:07:24.599 --> 00:07:27.590 mishmash of anything that went wrong
NOTE Confidence: 0.8542902

00:07:27.590 --> 00:07:29.702 with cardiac development prenatally.
NOTE Confidence: 0.8542902

00:07:29.710 --> 00:07:32.310 So what we really need to do is
NOTE Confidence: 0.8542902

00:07:32.310 --> 00:07:34.662 increase the number of patients that
NOTE Confidence: 0.8542902

00:07:34.662 --> 00:07:37.609 we have sequenced and this goes into
NOTE Confidence: 0.8542902

00:07:37.609 --> 00:07:40.183 the whole issue of genomic health
NOTE Confidence: 0.8542902

00:07:40.183 --> 00:07:42.170 and recruitment and sequencing
NOTE Confidence: 0.8542902

00:07:42.170 --> 00:07:45.670 of really large patient cohorts.
NOTE Confidence: 0.8542902

00:07:45.670 --> 00:07:48.238 I took a first step together with the
NOTE Confidence: 0.8542902

00:07:48.238 --> 00:07:50.229 Yale Center for Genome Analysis because
NOTE Confidence: 0.8542902

00:07:50.229 --> 00:07:53.397 as you can see on the table on the left,

NOTE Confidence: 0.8542902

00:07:53.400 --> 00:07:55.326 the cost of a whole exon.

NOTE Confidence: 0.8542902

00:07:55.330 --> 00:07:57.269 When we did this was 140 actually

NOTE Confidence: 0.8542902

00:07:57.269 --> 00:07:59.946 was at one point it was \$200 and so

NOTE Confidence: 0.8542902

00:07:59.946 --> 00:08:02.354 the limitation was not the number of

NOTE Confidence: 0.8542902

00:08:02.354 --> 00:08:04.664 patients who were willing to participate,

NOTE Confidence: 0.8542902

00:08:04.670 --> 00:08:06.356 but just the number of dollars

NOTE Confidence: 0.8542902

00:08:06.356 --> 00:08:08.529 we had to do the sequencing.

NOTE Confidence: 0.8542902

00:08:08.530 --> 00:08:09.496 So Michael Serrant,

NOTE Confidence: 0.8542902

00:08:09.496 --> 00:08:10.784 who's a graduate student,

NOTE Confidence: 0.8542902

00:08:10.790 --> 00:08:11.506 said, OK,

NOTE Confidence: 0.8542902

00:08:11.506 --> 00:08:13.654 I'm going to develop a targeted

NOTE Confidence: 0.8542902

00:08:13.654 --> 00:08:14.980 sequencing approach that allows

NOTE Confidence: 0.8542902

00:08:14.980 --> 00:08:16.898 us to get all the best guests.

NOTE Confidence: 0.8542902

00:08:16.900 --> 00:08:18.520 Congenital heart disease genes.

NOTE Confidence: 0.8542902

00:08:18.520 --> 00:08:20.545 In a lot of patients,

NOTE Confidence: 0.8542902

00:08:20.550 --> 00:08:22.840 for a very low cost,
NOTE Confidence: 0.8542902

00:08:22.840 --> 00:08:24.109 \$37 a sample.
NOTE Confidence: 0.8542902

00:08:24.109 --> 00:08:27.070 He did this with molecular inversion probe
NOTE Confidence: 0.8542902

00:08:27.147 --> 00:08:30.165 sequencing that's outlined on the right.
NOTE Confidence: 0.8542902

00:08:30.170 --> 00:08:32.906 This panel included 248 known and
NOTE Confidence: 0.8542902

00:08:32.906 --> 00:08:35.210 putative congenital heart disease genes,
NOTE Confidence: 0.8542902

00:08:35.210 --> 00:08:38.506 and he was able to do a statistically
NOTE Confidence: 0.8542902

00:08:38.506 --> 00:08:40.524 robust meta analysis combining
NOTE Confidence: 0.8542902

00:08:40.524 --> 00:08:43.854 our whole exon data and the
NOTE Confidence: 0.8542902

00:08:43.854 --> 00:08:46.233 targeted sequencing data so that
NOTE Confidence: 0.8542902

00:08:46.233 --> 00:08:48.998 now he has genomic data on 11,000.
NOTE Confidence: 0.8542902

00:08:49.000 --> 00:08:51.120 500 programs with congenital heart
NOTE Confidence: 0.8542902

00:08:51.120 --> 00:08:53.700 disease and this really lets us
NOTE Confidence: 0.8542902

00:08:53.700 --> 00:08:55.650 see what expanding cohort size
NOTE Confidence: 0.8542902

00:08:55.650 --> 00:08:57.955 and expanding the amount of data
NOTE Confidence: 0.8542902

00:08:57.955 --> 00:08:59.635 we have available in forms,

NOTE Confidence: 0.8542902

00:08:59.640 --> 00:09:01.980 so we were able to increase

NOTE Confidence: 0.8542902

00:09:01.980 --> 00:09:04.369 from a small number of genes.

NOTE Confidence: 0.8542902

00:09:04.370 --> 00:09:06.944 The genes that are underlined here

NOTE Confidence: 0.8542902

00:09:06.944 --> 00:09:08.660 that had significant statistical

NOTE Confidence: 0.8542902

00:09:08.729 --> 00:09:10.805 validation of a role in congenital

NOTE Confidence: 0.8542902

00:09:10.805 --> 00:09:12.189 heart disease to 61

NOTE Confidence: 0.8642125

00:09:12.255 --> 00:09:14.830 jeans, and this is by increasing from

NOTE Confidence: 0.8642125

00:09:14.830 --> 00:09:16.970 2700 programs to 11,000 programs.

NOTE Confidence: 0.8642125

00:09:16.970 --> 00:09:20.130 Now remember this is only across 248 genes,

NOTE Confidence: 0.8642125

00:09:20.130 --> 00:09:21.534 so there's still.

NOTE Confidence: 0.8642125

00:09:21.534 --> 00:09:24.810 A lot of room to learn more.

NOTE Confidence: 0.8642125

00:09:24.810 --> 00:09:27.370 The other thing is this is across the

NOTE Confidence: 0.8642125

00:09:27.370 --> 00:09:29.907 broad range of congenital heart disease.

NOTE Confidence: 0.8642125

00:09:29.910 --> 00:09:31.884 However, having this very large cohort

NOTE Confidence: 0.8642125

00:09:31.884 --> 00:09:34.651 now allows us to separate the genes to

NOTE Confidence: 0.8642125

00:09:34.651 --> 00:09:36.733 those that provide risk for specific
NOTE Confidence: 0.8642125

00:09:36.795 --> 00:09:39.010 subtypes of congenital heart disease.
NOTE Confidence: 0.8642125

00:09:39.010 --> 00:09:39.684 For instance,
NOTE Confidence: 0.8642125

00:09:39.684 --> 00:09:42.380 you can see on the right that the
NOTE Confidence: 0.8642125

00:09:42.458 --> 00:09:44.612 jeans flip for Jaguar include H
NOTE Confidence: 0.8642125

00:09:44.612 --> 00:09:47.642 and TBX really put you at risk for
NOTE Confidence: 0.8642125

00:09:47.642 --> 00:09:49.922 developing a type of congenital heart
NOTE Confidence: 0.8642125

00:09:49.930 --> 00:09:51.750 disease called tetralogy of fellow.
NOTE Confidence: 0.8642125

00:09:51.750 --> 00:09:54.046 And when you look even more carefully
NOTE Confidence: 0.8642125

00:09:54.046 --> 00:09:56.239 you can now submit segregate.
NOTE Confidence: 0.8642125

00:09:56.240 --> 00:09:58.585 Those patients to identify the patients that,
NOTE Confidence: 0.8642125

00:09:58.590 --> 00:09:59.320 for instance,
NOTE Confidence: 0.8642125

00:09:59.320 --> 00:10:01.510 are at high risk for neurodevelopmental
NOTE Confidence: 0.8642125

00:10:01.510 --> 00:10:03.277 abnormalities and those that are not.
NOTE Confidence: 0.8642125

00:10:03.280 --> 00:10:05.205 You can see that these genes on
NOTE Confidence: 0.8642125

00:10:05.205 --> 00:10:07.734 the right are the ones that have

NOTE Confidence: 0.8642125

00:10:07.734 --> 00:10:08.964 very specific contributions.

NOTE Confidence: 0.8642125

00:10:08.970 --> 00:10:10.790 The ones on the left are genes

NOTE Confidence: 0.8642125

00:10:10.790 --> 00:10:12.728 that are more globally involved in

NOTE Confidence: 0.8642125

00:10:12.728 --> 00:10:14.924 heart development and cause a broad

NOTE Confidence: 0.8642125

00:10:14.924 --> 00:10:17.007 range of congenital heart disease.

NOTE Confidence: 0.8642125

00:10:17.010 --> 00:10:18.250 And we're now hypothesising,

NOTE Confidence: 0.8642125

00:10:18.250 --> 00:10:20.110 but some of these changes may

NOTE Confidence: 0.8642125

00:10:20.168 --> 00:10:21.948 actually affect more than cardiac

NOTE Confidence: 0.8642125

00:10:21.948 --> 00:10:23.372 structure may also affect,

NOTE Confidence: 0.8642125

00:10:23.380 --> 00:10:24.226 for instance,

NOTE Confidence: 0.8642125

00:10:24.226 --> 00:10:26.341 that progressive risk for myocardial

NOTE Confidence: 0.8642125

00:10:26.341 --> 00:10:28.170 dysfunction over patients lifetime.

NOTE Confidence: 0.8642125

00:10:28.170 --> 00:10:30.492 So what do these discoveries from

NOTE Confidence: 0.8642125

00:10:30.492 --> 00:10:33.568 genomic analysis do to inform clinical care?

NOTE Confidence: 0.8642125

00:10:33.570 --> 00:10:36.054 And here's an example from the

NOTE Confidence: 0.8642125

00:10:36.054 --> 00:10:37.296 Yale Health System,
NOTE Confidence: 0.8642125

00:10:37.300 --> 00:10:39.916 a 2 month old ex pre term infant
NOTE Confidence: 0.8642125

00:10:39.916 --> 00:10:41.532 was transferred for hepatic
NOTE Confidence: 0.8642125

00:10:41.532 --> 00:10:43.747 failure and liver transplant and
NOTE Confidence: 0.8642125

00:10:43.747 --> 00:10:46.131 the liver transplant team obtained
NOTE Confidence: 0.8642125

00:10:46.131 --> 00:10:48.087 rapid whole exome sequencing.
NOTE Confidence: 0.8642125

00:10:48.090 --> 00:10:50.580 Patient also had congenital heart disease,
NOTE Confidence: 0.8642125

00:10:50.580 --> 00:10:51.825 atrioventricular canal and
NOTE Confidence: 0.8642125

00:10:51.825 --> 00:10:53.485 repeating ductus arterio sis,
NOTE Confidence: 0.8642125

00:10:53.490 --> 00:10:55.968 although that particular type of congenital
NOTE Confidence: 0.8642125

00:10:55.968 --> 00:10:58.540 heart disease should not have resulted.
NOTE Confidence: 0.8642125

00:10:58.540 --> 00:11:00.900 In this degree of distress at this age,
NOTE Confidence: 0.8642125

00:11:00.900 --> 00:11:04.820 here is an outline of the heart disease.
NOTE Confidence: 0.8642125

00:11:04.820 --> 00:11:06.614 An extensive metabolic work up was
NOTE Confidence: 0.8642125

00:11:06.614 --> 00:11:09.554 done to show A cause for the hepatic
NOTE Confidence: 0.8642125

00:11:09.554 --> 00:11:11.654 failure yielded nothing exon sequencing,

NOTE Confidence: 0.8642125

00:11:11.660 --> 00:11:14.276 which why SGA turned over in five days

NOTE Confidence: 0.8642125

00:11:14.276 --> 00:11:16.609 revealed a loss of function mutation

NOTE Confidence: 0.8642125

00:11:16.609 --> 00:11:19.220 in a chromatin modifier called CHD 7.

NOTE Confidence: 0.8642125

00:11:19.220 --> 00:11:21.080 This mutation was diagnostic for

NOTE Confidence: 0.8642125

00:11:21.080 --> 00:11:22.568 something called Charge syndrome

NOTE Confidence: 0.8642125

00:11:22.568 --> 00:11:24.620 which nobody thought the patient had.

NOTE Confidence: 0.8642125

00:11:24.620 --> 00:11:26.951 This is the list of the particular

NOTE Confidence: 0.8642125

00:11:26.951 --> 00:11:28.580 features of Charge syndrome.

NOTE Confidence: 0.8642125

00:11:28.580 --> 00:11:30.020 A coloboma choanal atresia.

NOTE Confidence: 0.8642125

00:11:30.020 --> 00:11:31.820 These are usually quite obvious.

NOTE Confidence: 0.8642125

00:11:31.820 --> 00:11:33.980 Patient didn't have any of those.

NOTE Confidence: 0.8642125

00:11:33.980 --> 00:11:36.980 The only things he had was heart defect.

NOTE Confidence: 0.8642125

00:11:36.980 --> 00:11:39.104 He had somewhat unusual looking external

NOTE Confidence: 0.8642125

00:11:39.104 --> 00:11:41.788 ears and a C HD7 gene mutation.

NOTE Confidence: 0.82228494

00:11:44.010 --> 00:11:46.618 And then we did a literature search on

NOTE Confidence: 0.82228494

00:11:46.618 --> 00:11:48.908 liver function in charge syndrome and found

NOTE Confidence: 0.82228494

00:11:48.908 --> 00:11:51.359 not a single report of liver abnormalities

NOTE Confidence: 0.82228494

00:11:51.359 --> 00:11:53.807 or liver failure in that setting.

NOTE Confidence: 0.82228494

00:11:53.810 --> 00:11:56.178 So the thought began to percolate to the

NOTE Confidence: 0.82228494

00:11:56.178 --> 00:11:58.710 top that this patient actually was much

NOTE Confidence: 0.82228494

00:11:58.710 --> 00:12:01.016 more affected by the congenital heart

NOTE Confidence: 0.82228494

00:12:01.016 --> 00:12:03.606 disease than primary liver disease went to.

NOTE Confidence: 0.82228494

00:12:03.610 --> 00:12:05.140 The Cath lab,

NOTE Confidence: 0.82228494

00:12:05.140 --> 00:12:08.200 had the patent ductus arteriosus closed.

NOTE Confidence: 0.82228494

00:12:08.200 --> 00:12:09.950 And within about five days,

NOTE Confidence: 0.82228494

00:12:09.950 --> 00:12:11.246 hepatic function started returning

NOTE Confidence: 0.82228494

00:12:11.246 --> 00:12:13.190 to normal in the patient was

NOTE Confidence: 0.82228494

00:12:13.244 --> 00:12:15.199 discharged without a liver transplant.

NOTE Confidence: 0.82228494

00:12:15.200 --> 00:12:17.456 So this kind of highlights how

NOTE Confidence: 0.82228494

00:12:17.456 --> 00:12:19.655 knowing the genetics lets you predict

NOTE Confidence: 0.82228494

00:12:19.655 --> 00:12:21.846 what a patient is at risk for,

NOTE Confidence: 0.82228494

00:12:21.850 --> 00:12:24.674 but also lets you predict maybe what a

NOTE Confidence: 0.82228494

00:12:24.674 --> 00:12:27.619 patient is not at risk for and provides

NOTE Confidence: 0.82228494

00:12:27.619 --> 00:12:30.022 a more objective lens through which

NOTE Confidence: 0.82228494

00:12:30.022 --> 00:12:33.109 clinicians can view how patient is doing.

NOTE Confidence: 0.82228494

00:12:33.110 --> 00:12:35.273 Was this just an isolated patient or

NOTE Confidence: 0.82228494

00:12:35.273 --> 00:12:37.726 a more global finding an answer from

NOTE Confidence: 0.82228494

00:12:37.726 --> 00:12:39.916 the large sequencing effort from the

NOTE Confidence: 0.82228494

00:12:39.979 --> 00:12:42.652 PC GC where we did look at those 11,000

NOTE Confidence: 0.82228494

00:12:42.652 --> 00:12:44.475 patients is that this is actually

NOTE Confidence: 0.82228494

00:12:44.475 --> 00:12:46.560 much more common than we thought,

NOTE Confidence: 0.82228494

00:12:46.560 --> 00:12:48.856 so this list is all the patients

NOTE Confidence: 0.82228494

00:12:48.856 --> 00:12:49.840 that we found.

NOTE Confidence: 0.82228494

00:12:49.840 --> 00:12:51.634 A molecular charge diagnosis and the

NOTE Confidence: 0.82228494

00:12:51.634 --> 00:12:54.100 ones up top had a clinical diagnosis.

NOTE Confidence: 0.82228494

00:12:54.100 --> 00:12:56.396 The ones on the bottom do not.

NOTE Confidence: 0.82228494

00:12:56.400 --> 00:12:58.782 There is nothing about their mutations
NOTE Confidence: 0.82228494

00:12:58.782 --> 00:13:01.187 that predicts they will fall into
NOTE Confidence: 0.82228494

00:13:01.187 --> 00:13:03.047 the clinical charge diagnosis or
NOTE Confidence: 0.82228494

00:13:03.047 --> 00:13:05.319 the no clinical charge diagnosis.
NOTE Confidence: 0.82228494

00:13:05.320 --> 00:13:08.057 If you look at their phenotypic spectrum,
NOTE Confidence: 0.82228494

00:13:08.060 --> 00:13:10.400 the ones with the molecular diagnosis.
NOTE Confidence: 0.82228494

00:13:10.400 --> 00:13:12.355 Obviously since the entrance mechanism
NOTE Confidence: 0.82228494

00:13:12.355 --> 00:13:14.310 here was congenital heart disease,
NOTE Confidence: 0.82228494

00:13:14.310 --> 00:13:17.047 100% of them had congenital heart disease,
NOTE Confidence: 0.82228494

00:13:17.050 --> 00:13:20.058 but a much smaller number had the other
NOTE Confidence: 0.82228494

00:13:20.058 --> 00:13:22.130 expected findings of charge syndrome,
NOTE Confidence: 0.82228494

00:13:22.130 --> 00:13:25.040 and So what I think we're at now is that
NOTE Confidence: 0.82228494

00:13:25.117 --> 00:13:27.433 a molecular diagnosis is a prediction
NOTE Confidence: 0.82228494

00:13:27.433 --> 00:13:30.011 of risks and is somewhat different
NOTE Confidence: 0.82228494

00:13:30.011 --> 00:13:32.411 from the old clinical diagnosis
NOTE Confidence: 0.82228494

00:13:32.411 --> 00:13:35.285 that were based on very specific,

NOTE Confidence: 0.82228494

00:13:35.285 --> 00:13:37.185 well defined clinical findings.

NOTE Confidence: 0.82228494

00:13:37.190 --> 00:13:38.270 These molecular diagnosis,

NOTE Confidence: 0.82228494

00:13:38.270 --> 00:13:39.710 especially if they're returned

NOTE Confidence: 0.82228494

00:13:39.710 --> 00:13:40.430 rapidly enough,

NOTE Confidence: 0.82228494

00:13:40.430 --> 00:13:42.038 can really significantly inform

NOTE Confidence: 0.82228494

00:13:42.038 --> 00:13:44.855 patient care and give us some guidance

NOTE Confidence: 0.82228494

00:13:44.855 --> 00:13:47.543 as to what are the risks that that

NOTE Confidence: 0.82228494

00:13:47.543 --> 00:13:49.069 patient is going to face.

NOTE Confidence: 0.82228494

00:13:49.070 --> 00:13:51.583 What are some of the things we

NOTE Confidence: 0.82228494

00:13:51.583 --> 00:13:54.621 should look for or not look for

NOTE Confidence: 0.82228494

00:13:54.621 --> 00:13:56.497 and significantly enhance patient

NOTE Confidence: 0.82228494

00:13:56.497 --> 00:13:58.140 care going forward?

NOTE Confidence: 0.82228494

00:13:58.140 --> 00:14:00.100 So where do we go from here?

NOTE Confidence: 0.82228494

00:14:00.100 --> 00:14:02.025 The diagram on the left is what

NOTE Confidence: 0.82228494

00:14:02.025 --> 00:14:03.180 we know so far,

NOTE Confidence: 0.82228494

00:14:03.180 --> 00:14:05.316 and what we've really learned over
NOTE Confidence: 0.82228494

00:14:05.316 --> 00:14:07.720 the last 11 years of participating
NOTE Confidence: 0.82228494

00:14:07.720 --> 00:14:09.076 in this project.
NOTE Confidence: 0.82228494

00:14:09.080 --> 00:14:11.105 56% of congenital heart disease
NOTE Confidence: 0.82228494

00:14:11.105 --> 00:14:13.130 still has an unknown cause,
NOTE Confidence: 0.82228494

00:14:13.130 --> 00:14:16.410 and so we really need to go after
NOTE Confidence: 0.82228494

00:14:16.410 --> 00:14:19.139 this more challenging aspect.
NOTE Confidence: 0.82228494

00:14:19.140 --> 00:14:21.618 These could be due to rare common
NOTE Confidence: 0.82228494

00:14:21.618 --> 00:14:22.326 variant interactions,
NOTE Confidence: 0.82228494

00:14:22.330 --> 00:14:24.100 recessive contribution across the genome,
NOTE Confidence: 0.82228494

00:14:24.100 --> 00:14:25.870 Multigenic contribution and contribution of.
NOTE Confidence: 0.82228494

00:14:25.870 --> 00:14:28.372 Then we are also interested in
NOTE Confidence: 0.82228494

00:14:28.372 --> 00:14:30.482 looking at the contribution of
NOTE Confidence: 0.82228494

00:14:30.482 --> 00:14:32.337 the genetic data to outcome.
NOTE Confidence: 0.82228494

00:14:32.340 --> 00:14:33.544 But to do this,
NOTE Confidence: 0.82228494

00:14:33.544 --> 00:14:35.350 you really need to expand the

NOTE Confidence: 0.82228494

00:14:35.418 --> 00:14:37.824 genomic data and why SGA has

NOTE Confidence: 0.82228494

00:14:37.824 --> 00:14:39.428 recently very generously agreed

NOTE Confidence: 0.82228494

00:14:39.499 --> 00:14:41.639 to lower their sequencing rates.

NOTE Confidence: 0.82228494

00:14:41.640 --> 00:14:45.150 So now we can really get whole exomes on

NOTE Confidence: 0.82228494

00:14:45.150 --> 00:14:47.957 everybody and don't need to focus on it.

NOTE Confidence: 0.82228494

00:14:47.960 --> 00:14:49.480 Targeted 100 and 248 genes

NOTE Confidence: 0.82228494

00:14:49.480 --> 00:14:51.000 we're going to be doing

NOTE Confidence: 0.8218752

00:14:51.064 --> 00:14:52.444 7000 additional probands

NOTE Confidence: 0.8218752

00:14:52.444 --> 00:14:54.284 with whole exome sequencing,

NOTE Confidence: 0.8218752

00:14:54.290 --> 00:14:57.071 so this is really going to be the largest

NOTE Confidence: 0.8218752

00:14:57.071 --> 00:14:59.119 sequence congenital disease cohorts.

NOTE Confidence: 0.8218752

00:14:59.120 --> 00:15:00.716 These patients are also

NOTE Confidence: 0.8218752

00:15:00.716 --> 00:15:03.110 going to get sniper a data.

NOTE Confidence: 0.8218752

00:15:03.110 --> 00:15:05.100 And we're hoping that as

NOTE Confidence: 0.8218752

00:15:05.100 --> 00:15:06.692 sequencing modalities get more

NOTE Confidence: 0.8218752

00:15:06.692 --> 00:15:08.630 efficient and more cost effective,
NOTE Confidence: 0.8218752

00:15:08.630 --> 00:15:10.994 and we're able to recruit more
NOTE Confidence: 0.8218752

00:15:10.994 --> 00:15:12.570 patients across the country,
NOTE Confidence: 0.8218752

00:15:12.570 --> 00:15:14.789 we're going to be able to expand
NOTE Confidence: 0.8218752

00:15:14.789 --> 00:15:17.484 this cohort to a large enough size
NOTE Confidence: 0.8218752

00:15:17.484 --> 00:15:19.574 to really start drawing genotype
NOTE Confidence: 0.8218752

00:15:19.574 --> 00:15:21.363 phenotype correlations and defining
NOTE Confidence: 0.8218752

00:15:21.363 --> 00:15:24.387 some of the more complex genetics that
NOTE Confidence: 0.8218752

00:15:24.390 --> 00:15:26.730 probably underlie the large part of
NOTE Confidence: 0.8218752

00:15:26.730 --> 00:15:28.720 the congenital heart disease cases.
NOTE Confidence: 0.8218752

00:15:28.720 --> 00:15:29.472 In addition,
NOTE Confidence: 0.8218752

00:15:29.472 --> 00:15:30.976 the pediatric Cardiac Genomics
NOTE Confidence: 0.8218752

00:15:30.976 --> 00:15:33.140 Consortium is involved in developing.
NOTE Confidence: 0.8218752

00:15:33.140 --> 00:15:36.188 Links between the genomic data and
NOTE Confidence: 0.8218752

00:15:36.188 --> 00:15:38.220 the electronic medical records,
NOTE Confidence: 0.8218752

00:15:38.220 --> 00:15:41.490 and this is being done collaboratively

NOTE Confidence: 0.8218752

00:15:41.490 --> 00:15:45.708 with Mike Murray and a group at

NOTE Confidence: 0.8218752

00:15:45.708 --> 00:15:47.649 Cincinnati Children's Hospital.

NOTE Confidence: 0.8218752

00:15:47.650 --> 00:15:50.359 So I want to thank the people

NOTE Confidence: 0.8218752

00:15:50.359 --> 00:15:52.449 that did all the work,

NOTE Confidence: 0.8218752

00:15:52.450 --> 00:15:54.835 in particular the patients and

NOTE Confidence: 0.8218752

00:15:54.835 --> 00:15:56.743 families who generously contributed

NOTE Confidence: 0.8218752

00:15:56.743 --> 00:15:58.906 their information and their genomic

NOTE Confidence: 0.8218752

00:15:58.906 --> 00:16:01.330 sample and data to this project

NOTE Confidence: 0.8218752

00:16:01.400 --> 00:16:03.535 and a special hands up for the

NOTE Confidence: 0.8218752

00:16:03.535 --> 00:16:05.250 Yale Center for Genome Analysis,

NOTE Confidence: 0.8218752

00:16:05.250 --> 00:16:06.450 CIAM and Shrikant,

NOTE Confidence: 0.8218752

00:16:06.450 --> 00:16:08.682 who have been incredibly involved with

NOTE Confidence: 0.8218752

00:16:08.682 --> 00:16:10.850 this project since its inception.

NOTE Confidence: 0.8218752

00:16:10.850 --> 00:16:12.850 It was initially driven by

NOTE Confidence: 0.8218752

00:16:12.850 --> 00:16:14.880 Rick Lifton's idea that, hey,

NOTE Confidence: 0.8218752

00:16:14.880 --> 00:16:18.320 this has to be a de Novo mechanism.

NOTE Confidence: 0.8218752

00:16:18.320 --> 00:16:21.068 Ann has evolved significantly since then.

NOTE Confidence: 0.8218752

00:16:21.070 --> 00:16:23.395 I'm happy to take questions

NOTE Confidence: 0.8218752

00:16:23.395 --> 00:16:26.221 by email or by chat box.