

WEBVTT

NOTE duration:"00:19:00"

NOTE recognizability:0.859

NOTE language:en-us

NOTE Confidence: 0.82244659

00:00:12.840 --> 00:00:15.025 Welcome back to Yale Liver

NOTE Confidence: 0.82244659

00:00:15.025 --> 00:00:16.336 Diamond Jubilee event.

NOTE Confidence: 0.82244659

00:00:16.340 --> 00:00:18.090 The Q&A for the afternoon

NOTE Confidence: 0.82244659

00:00:18.090 --> 00:00:20.240 sessions will take place at 3:15.

NOTE Confidence: 0.82244659

00:00:20.240 --> 00:00:21.970 This session is being recorded.

NOTE Confidence: 0.82244659

00:00:21.970 --> 00:00:25.850 Thank you. Welcome to our the

NOTE Confidence: 0.82244659

00:00:25.850 --> 00:00:27.980 second talk in our series and

NOTE Confidence: 0.82244659

00:00:28.058 --> 00:00:30.500 I'm Cliff boat and I'm proud

NOTE Confidence: 0.82244659

00:00:30.500 --> 00:00:32.128 to introduce Prim mystery,

NOTE Confidence: 0.82244659

00:00:32.130 --> 00:00:34.224 who's professor of medicine at the

NOTE Confidence: 0.82244659

00:00:34.224 --> 00:00:36.471 Yale School of Medicine and director

NOTE Confidence: 0.82244659

00:00:36.471 --> 00:00:38.446 of the Lysosomal Disease program,

NOTE Confidence: 0.82244659

00:00:38.450 --> 00:00:40.208 and he'll be speaking to us

NOTE Confidence: 0.82244659

00:00:40.208 --> 00:00:41.952 today around on rare metabolic
NOTE Confidence: 0.82244659

00:00:41.952 --> 00:00:43.630 and undiagnosed diseases.
NOTE Confidence: 0.844619876666667

00:00:49.500 --> 00:00:52.285 Thank you so much Cliff
NOTE Confidence: 0.844619876666667

00:00:52.285 --> 00:00:54.513 for your kind introduction.
NOTE Confidence: 0.844619876666667

00:00:54.520 --> 00:00:57.901 I want to thank Michael Nathanson and
NOTE Confidence: 0.844619876666667

00:00:57.901 --> 00:01:00.330 Mario Strasser Bosco for including
NOTE Confidence: 0.844619876666667

00:01:00.330 --> 00:01:02.780 the topic of friend metabolic
NOTE Confidence: 0.844619876666667

00:01:02.780 --> 00:01:05.303 and undiagnosed liver diseases in
NOTE Confidence: 0.844619876666667

00:01:05.303 --> 00:01:07.728 the time and Jubilee celebration.
NOTE Confidence: 0.844619876666667

00:01:07.730 --> 00:01:10.898 It is appropriate to start with our founder.
NOTE Confidence: 0.95854423

00:01:13.140 --> 00:01:15.380 I want to go to the next slide.
NOTE Confidence: 0.95854423

00:01:15.380 --> 00:01:17.790 It is appropriate for us
NOTE Confidence: 0.95854423

00:01:17.790 --> 00:01:20.200 to start with our founder.
NOTE Confidence: 0.95854423

00:01:20.200 --> 00:01:21.612 Who was affectionately called
NOTE Confidence: 0.95854423

00:01:21.612 --> 00:01:23.377 by his colleagues at Yale,
NOTE Confidence: 0.95854423

00:01:23.380 --> 00:01:26.506 New Haven Hospital and his students

NOTE Confidence: 0.95854423

00:01:26.506 --> 00:01:29.040 as General Classic and DRD.

NOTE Confidence: 0.95854423

00:01:29.040 --> 00:01:31.750 The Doctor of rare diseases.

NOTE Confidence: 0.95854423

00:01:31.750 --> 00:01:34.270 His renowned clinical acumen was

NOTE Confidence: 0.95854423

00:01:34.270 --> 00:01:37.425 underpinned by his ability to treasure

NOTE Confidence: 0.95854423

00:01:37.425 --> 00:01:40.150 the exceptions in his clinical

NOTE Confidence: 0.95854423

00:01:40.150 --> 00:01:42.999 practice annunciated by the renowned

NOTE Confidence: 0.95854423

00:01:42.999 --> 00:01:46.485 British geneticist of early 20th century.

NOTE Confidence: 0.95854423

00:01:46.490 --> 00:01:48.745 The most dramatic illustration of

NOTE Confidence: 0.95854423

00:01:48.745 --> 00:01:51.418 the importance of this approach is

NOTE Confidence: 0.95854423

00:01:51.418 --> 00:01:53.500 the work of Brown and Goldstein.

NOTE Confidence: 0.95854423

00:01:53.500 --> 00:01:55.519 Who's stratified cholesterol

NOTE Confidence: 0.95854423

00:01:55.519 --> 00:01:58.884 syndromes and found the exceptional

NOTE Confidence: 0.95854423

00:01:58.884 --> 00:02:02.170 patients and discovered LDL receptor

NOTE Confidence: 0.95854423

00:02:02.170 --> 00:02:05.075 using skin fibroblast cell lines.

NOTE Confidence: 0.95854423

00:02:05.075 --> 00:02:08.555 One year after they won the Nobel Prize,

NOTE Confidence: 0.95854423

00:02:08.560 --> 00:02:11.290 Joe Goldstein in his presidential
NOTE Confidence: 0.95854423

00:02:11.290 --> 00:02:14.240 address to the American Society of
NOTE Confidence: 0.95854423

00:02:14.240 --> 00:02:16.160 Clinical Investigation bemoaned the
NOTE Confidence: 0.95854423

00:02:16.160 --> 00:02:18.849 plight of academic investigators and
NOTE Confidence: 0.95854423

00:02:18.849 --> 00:02:21.183 issued a prescription for the syndrome
NOTE Confidence: 0.95854423

00:02:21.183 --> 00:02:24.229 that he calls called paralyzed academic.
NOTE Confidence: 0.95854423

00:02:24.230 --> 00:02:25.946 Investigate the syndrome.
NOTE Confidence: 0.95854423

00:02:25.946 --> 00:02:29.378 And the prescription was to obtain
NOTE Confidence: 0.95854423

00:02:29.380 --> 00:02:31.423 technical scientific training
NOTE Confidence: 0.95854423

00:02:31.423 --> 00:02:34.147 and show technical courage.
NOTE Confidence: 0.95854423

00:02:34.150 --> 00:02:37.348 Implicit in this was the essential
NOTE Confidence: 0.95854423

00:02:37.348 --> 00:02:39.480 clinical skills to recognize
NOTE Confidence: 0.95854423

00:02:39.570 --> 00:02:42.280 the exceptional patient and now.
NOTE Confidence: 0.95854423

00:02:42.280 --> 00:02:45.598 Armed with the access to genomic analysis,
NOTE Confidence: 0.95854423

00:02:45.600 --> 00:02:48.694 every patient on our task in service
NOTE Confidence: 0.95854423

00:02:48.694 --> 00:02:51.970 and liver transplant service is such

NOTE Confidence: 0.95854423

00:02:51.970 --> 00:02:54.454 an exceptional patient displaying

NOTE Confidence: 0.95854423

00:02:54.454 --> 00:02:56.853 unique genetic vulnerabilities to

NOTE Confidence: 0.95854423

00:02:56.853 --> 00:02:59.118 develop end stage liver disease.

NOTE Confidence: 0.95854423

00:02:59.120 --> 00:03:02.195 This knowledge is transforming hepatology

NOTE Confidence: 0.95854423

00:03:02.195 --> 00:03:05.296 practice as vividly illustrated by

NOTE Confidence: 0.95854423

00:03:05.296 --> 00:03:08.753 Sylvia Villarino's Trail Brave trail,

NOTE Confidence: 0.95854423

00:03:08.753 --> 00:03:10.579 blazing world.

NOTE Confidence: 0.95854423

00:03:10.580 --> 00:03:13.548 I think Doctor Katzkin would be very proud

NOTE Confidence: 0.95854423

00:03:13.550 --> 00:03:17.330 to see that we have national destination

NOTE Confidence: 0.95854423

00:03:17.330 --> 00:03:20.220 programs in undiagnosed liver disease,

NOTE Confidence: 0.95854423

00:03:20.220 --> 00:03:21.554 Wilson's disease,

NOTE Confidence: 0.95854423

00:03:21.554 --> 00:03:22.888 lysosomal diseases,

NOTE Confidence: 0.95854423

00:03:22.888 --> 00:03:24.889 and inherited collegiality.

NOTE Confidence: 0.95854423

00:03:24.890 --> 00:03:27.755 But probably the world's largest

NOTE Confidence: 0.95854423

00:03:27.755 --> 00:03:30.620 biorepository and Natural History data.

NOTE Confidence: 0.95854423

00:03:30.620 --> 00:03:32.280 I was thinking about this.

NOTE Confidence: 0.88547971

00:03:34.830 --> 00:03:35.766 Oh, I'm sorry.

NOTE Confidence: 0.88547971

00:03:35.766 --> 00:03:37.638 One of my slides is missing.

NOTE Confidence: 0.88547971

00:03:37.640 --> 00:03:40.552 I was bragging about this to a

NOTE Confidence: 0.88547971

00:03:40.552 --> 00:03:42.691 colleague of mine and he asked

NOTE Confidence: 0.88547971

00:03:42.691 --> 00:03:45.174 me what are you going to do with

NOTE Confidence: 0.88547971

00:03:45.174 --> 00:03:47.496 all this and I've been thinking

NOTE Confidence: 0.88547971

00:03:47.496 --> 00:03:50.010 ever since about the question and

NOTE Confidence: 0.88547971

00:03:50.087 --> 00:03:52.810 asking how do we honor the immense

NOTE Confidence: 0.88547971

00:03:52.810 --> 00:03:55.422 gifts of patients that we follow

NOTE Confidence: 0.88547971

00:03:55.422 --> 00:03:57.702 providing Natural History data and

NOTE Confidence: 0.88547971

00:03:57.702 --> 00:04:00.036 bio samples to advanced clinical

NOTE Confidence: 0.88547971

00:04:00.036 --> 00:04:02.868 and basic science to benefit this

NOTE Confidence: 0.88547971

00:04:02.868 --> 00:04:04.769 underserved patient population.

NOTE Confidence: 0.88547971

00:04:04.770 --> 00:04:08.160 Who often feel neglected and

NOTE Confidence: 0.88547971

00:04:08.160 --> 00:04:09.516 deeply stigmatized?

NOTE Confidence: 0.88547971

00:04:09.520 --> 00:04:12.460 So right diseases are very important.

NOTE Confidence: 0.88547971

00:04:12.460 --> 00:04:15.298 They are defined as conditions that

NOTE Confidence: 0.88547971

00:04:15.298 --> 00:04:18.301 affect less than 200,000 people in

NOTE Confidence: 0.88547971

00:04:18.301 --> 00:04:20.936 the United States and collectively

NOTE Confidence: 0.88547971

00:04:20.936 --> 00:04:23.837 it affects one in ten Americans.

NOTE Confidence: 0.88547971

00:04:23.840 --> 00:04:27.319 Many of these disorders involve the liver,

NOTE Confidence: 0.88547971

00:04:27.320 --> 00:04:29.833 either as a primary site of metabolic

NOTE Confidence: 0.88547971

00:04:29.833 --> 00:04:33.140 defect or as part of Multisystemic disease,

NOTE Confidence: 0.88547971

00:04:33.140 --> 00:04:35.530 and typically patients see many

NOTE Confidence: 0.88547971

00:04:35.530 --> 00:04:37.920 different physicians up to about

NOTE Confidence: 0.88547971

00:04:37.998 --> 00:04:40.385 20 years with the mean of about.

NOTE Confidence: 0.88547971

00:04:40.390 --> 00:04:43.897 Five years to receive the correct diagnosis.

NOTE Confidence: 0.88547971

00:04:43.900 --> 00:04:46.184 Sadly, many remain undiagnosed,

NOTE Confidence: 0.88547971

00:04:46.184 --> 00:04:49.880 such as with diagnosis of natural D,

NOTE Confidence: 0.88547971

00:04:49.880 --> 00:04:51.896 even alcoholic liver disease,

NOTE Confidence: 0.88547971

00:04:51.896 --> 00:04:52.986 cryptogenic, cirrhosis.
NOTE Confidence: 0.88547971

00:04:52.986 --> 00:04:55.916 They remain a significant burden
NOTE Confidence: 0.88547971

00:04:55.916 --> 00:04:58.970 of hitherto unknown genetic phase
NOTE Confidence: 0.88547971

00:04:58.970 --> 00:05:01.478 syndromes causing liver disease,
NOTE Confidence: 0.88547971

00:05:01.480 --> 00:05:03.845 as is being exemplified by
NOTE Confidence: 0.88547971

00:05:03.845 --> 00:05:05.440 Sylvia Villarino's work.
NOTE Confidence: 0.88547971

00:05:05.440 --> 00:05:06.000 Importantly,
NOTE Confidence: 0.88547971

00:05:06.000 --> 00:05:09.360 what Brown and Goldstein taught us
NOTE Confidence: 0.88547971

00:05:09.360 --> 00:05:12.640 is that understanding rare diseases
NOTE Confidence: 0.88547971

00:05:12.640 --> 00:05:15.305 confers the ability to transform
NOTE Confidence: 0.88547971

00:05:15.305 --> 00:05:17.437 understanding of common diseases,
NOTE Confidence: 0.88547971

00:05:17.440 --> 00:05:20.060 such as with familial hypercholesterolemia,
NOTE Confidence: 0.88547971

00:05:20.060 --> 00:05:22.364 statins, and PCSK.
NOTE Confidence: 0.88547971

00:05:22.364 --> 00:05:23.900 9 inhibitors.
NOTE Confidence: 0.88547971

00:05:23.900 --> 00:05:25.820 So this was the slide I
NOTE Confidence: 0.88547971

00:05:25.820 --> 00:05:27.100 was talking to earlier,

NOTE Confidence: 0.88547971

00:05:27.100 --> 00:05:30.646 and so patients are coming to see us from

NOTE Confidence: 0.88547971

00:05:30.646 --> 00:05:33.983 all over the country year after year,

NOTE Confidence: 0.88547971

00:05:33.983 --> 00:05:35.907 allowing us to capture.

NOTE Confidence: 0.88547971

00:05:35.910 --> 00:05:39.483 Giving us the privilege to take care of them.

NOTE Confidence: 0.88547971

00:05:39.490 --> 00:05:41.958 Collecting Natural History data,

NOTE Confidence: 0.88547971

00:05:41.958 --> 00:05:43.809 providing bio samples.

NOTE Confidence: 0.88547971

00:05:43.810 --> 00:05:47.356 And I was bragging about this to a senior

NOTE Confidence: 0.88547971

00:05:47.356 --> 00:05:49.987 physician scientist and he said to me,

NOTE Confidence: 0.88547971

00:05:49.990 --> 00:05:50.309 well,

NOTE Confidence: 0.88547971

00:05:50.309 --> 00:05:52.542 what are you going to do with

NOTE Confidence: 0.88547971

00:05:52.542 --> 00:05:54.940 all this enormous gifts that are

NOTE Confidence: 0.88547971

00:05:54.940 --> 00:05:56.950 given to you by your patients?

NOTE Confidence: 0.88547971

00:05:56.950 --> 00:06:01.486 How are you going to honor these

NOTE Confidence: 0.88547971

00:06:01.486 --> 00:06:05.599 gifts and then translate that to?

NOTE Confidence: 0.88547971

00:06:05.599 --> 00:06:09.214 Important questions to advance clinical

NOTE Confidence: 0.88547971

00:06:09.214 --> 00:06:12.839 science and help these patients.
NOTE Confidence: 0.88547971

00:06:12.840 --> 00:06:16.115 So here is the overarching premise
NOTE Confidence: 0.88547971

00:06:16.115 --> 00:06:18.175 based on lysosomal disease
NOTE Confidence: 0.88547971

00:06:18.175 --> 00:06:20.804 program that is being further
NOTE Confidence: 0.88547971

00:06:20.804 --> 00:06:23.514 advanced by Sylvia Pellegrino in
NOTE Confidence: 0.88547971

00:06:23.514 --> 00:06:25.840 her undiagnosed disease program.
NOTE Confidence: 0.88547971

00:06:25.840 --> 00:06:28.810 We've taken chocos since message to
NOTE Confidence: 0.88547971

00:06:28.810 --> 00:06:31.353 heart with everything beginning and
NOTE Confidence: 0.88547971

00:06:31.353 --> 00:06:34.239 ending with our patients and reverse
NOTE Confidence: 0.88547971

00:06:34.239 --> 00:06:36.664 translation to assemble unparalleled
NOTE Confidence: 0.88547971

00:06:36.664 --> 00:06:40.552 expertise in murine and humanized models.
NOTE Confidence: 0.88547971

00:06:40.560 --> 00:06:41.203 Sidelines,
NOTE Confidence: 0.88547971

00:06:41.203 --> 00:06:44.418 including I PSC headlines and
NOTE Confidence: 0.88547971

00:06:44.418 --> 00:06:48.013 application of genomics single cell
NOTE Confidence: 0.88547971

00:06:48.013 --> 00:06:50.797 transcriptomics biomarker discovery,
NOTE Confidence: 0.88547971

00:06:50.800 --> 00:06:52.249 and clinical trials,

NOTE Confidence: 0.88547971

00:06:52.249 --> 00:06:54.512 as Michael Matthews, Nathansen described,

NOTE Confidence: 0.88547971

00:06:54.512 --> 00:06:56.136 the culture of men.

NOTE Confidence: 0.88547971

00:06:56.140 --> 00:06:58.996 Mentorship is in the very fabric

NOTE Confidence: 0.88547971

00:06:58.996 --> 00:07:02.098 of our center to train the next

NOTE Confidence: 0.88547971

00:07:02.098 --> 00:07:03.766 generation of physician scientists

NOTE Confidence: 0.88547971

00:07:03.766 --> 00:07:06.544 and to provide pastoral care of

NOTE Confidence: 0.88547971

00:07:06.544 --> 00:07:08.412 these gifted upcoming individuals

NOTE Confidence: 0.88547971

00:07:08.412 --> 00:07:10.690 in this challenging times,

NOTE Confidence: 0.88547971

00:07:10.690 --> 00:07:13.638 when these individuals better

NOTE Confidence: 0.88547971

00:07:13.638 --> 00:07:15.849 on disproportionate burden.

NOTE Confidence: 0.88547971

00:07:15.850 --> 00:07:18.682 And so the major themes of our rare

NOTE Confidence: 0.88547971

00:07:18.682 --> 00:07:20.349 metabolic and diagnosed living

NOTE Confidence: 0.88547971

00:07:20.349 --> 00:07:22.995 liver disease program is to achieve

NOTE Confidence: 0.88547971

00:07:22.995 --> 00:07:25.469 the best outcomes for patient.

NOTE Confidence: 0.88547971

00:07:25.470 --> 00:07:28.380 To provide compassionate holistic care

NOTE Confidence: 0.88547971

00:07:28.380 --> 00:07:32.110 and advocacy and compile disease registry.
NOTE Confidence: 0.88547971

00:07:32.110 --> 00:07:35.502 And it has to be high science driven
NOTE Confidence: 0.88547971

00:07:35.502 --> 00:07:37.749 involving advanced disease modeling,
NOTE Confidence: 0.88547971

00:07:37.750 --> 00:07:40.550 iterative translation to patients to
NOTE Confidence: 0.88547971

00:07:40.550 --> 00:07:43.350 overcome the known limitations of
NOTE Confidence: 0.874947232

00:07:43.430 --> 00:07:46.150 murine models and then generating.
NOTE Confidence: 0.874947232

00:07:46.150 --> 00:07:48.574 Biomarker discovery and validation
NOTE Confidence: 0.874947232

00:07:48.574 --> 00:07:51.604 in patience to enhance patient
NOTE Confidence: 0.874947232

00:07:51.604 --> 00:07:54.413 management and enrich clinical
NOTE Confidence: 0.874947232

00:07:54.413 --> 00:07:56.528 trials involving transcriptomics,
NOTE Confidence: 0.874947232

00:07:56.530 --> 00:07:59.730 proteomics and also hypothesis
NOTE Confidence: 0.874947232

00:07:59.730 --> 00:08:02.130 driven candidate biomarkers.
NOTE Confidence: 0.874947232

00:08:02.130 --> 00:08:04.251 We are applying all mixed to investigate
NOTE Confidence: 0.874947232

00:08:04.251 --> 00:08:06.707 all of the disease beyond the liver.
NOTE Confidence: 0.874947232

00:08:06.710 --> 00:08:08.470 For example, the brain.
NOTE Confidence: 0.874947232

00:08:08.470 --> 00:08:11.110 I think when a hepatologist looks,

NOTE Confidence: 0.874947232

00:08:11.110 --> 00:08:14.482 for example at neuroinflammation

NOTE Confidence: 0.874947232

00:08:14.482 --> 00:08:16.684 or neurodegeneration using

NOTE Confidence: 0.874947232

00:08:16.684 --> 00:08:18.226 the current technologies,

NOTE Confidence: 0.874947232

00:08:18.226 --> 00:08:22.405 I believe that we bring the very special

NOTE Confidence: 0.874947232

00:08:22.405 --> 00:08:25.423 insight that cannot be provided if

NOTE Confidence: 0.874947232

00:08:25.423 --> 00:08:28.715 this components of the disease are

NOTE Confidence: 0.874947232

00:08:28.715 --> 00:08:30.982 studied by different specialities.

NOTE Confidence: 0.874947232

00:08:30.982 --> 00:08:34.534 And we provide the entire repertoire

NOTE Confidence: 0.874947232

00:08:34.534 --> 00:08:37.900 of therapies for genetic diseases,

NOTE Confidence: 0.874947232

00:08:37.900 --> 00:08:39.622 including liver transplantation

NOTE Confidence: 0.874947232

00:08:39.622 --> 00:08:41.918 and surgical gene therapy,

NOTE Confidence: 0.874947232

00:08:41.920 --> 00:08:44.476 but also gene therapies,

NOTE Confidence: 0.874947232

00:08:44.476 --> 00:08:47.032 including RNA and recombinant

NOTE Confidence: 0.874947232

00:08:47.032 --> 00:08:49.960 enzymes and small molecules.

NOTE Confidence: 0.874947232

00:08:49.960 --> 00:08:52.767 I think an area that I'm very

NOTE Confidence: 0.874947232

00:08:52.767 --> 00:08:55.001 excited about is the relevance

NOTE Confidence: 0.874947232

00:08:55.001 --> 00:08:58.114 of our rare disease endeavor to

NOTE Confidence: 0.874947232

00:08:58.114 --> 00:09:01.124 provide novel insights into disease

NOTE Confidence: 0.874947232

00:09:01.124 --> 00:09:03.727 mechanisms and novel therapeutic

NOTE Confidence: 0.874947232

00:09:03.727 --> 00:09:06.559 targets for common diseases.

NOTE Confidence: 0.874947232

00:09:06.560 --> 00:09:08.800 And so let's start with clinical care,

NOTE Confidence: 0.874947232

00:09:08.800 --> 00:09:11.005 and this is a paper that is about to

NOTE Confidence: 0.874947232

00:09:11.005 --> 00:09:13.228 be submitted from the International

NOTE Confidence: 0.874947232

00:09:13.228 --> 00:09:16.910 Group share registry that that shows

NOTE Confidence: 0.874947232

00:09:16.910 --> 00:09:20.660 extraordinarily high risk of cancer.

NOTE Confidence: 0.874947232

00:09:20.660 --> 00:09:23.240 It is for hematological cancers,

NOTE Confidence: 0.874947232

00:09:23.240 --> 00:09:24.731 including multiple myeloma

NOTE Confidence: 0.874947232

00:09:24.731 --> 00:09:26.719 and non Hodgkin's lymphoma.

NOTE Confidence: 0.874947232

00:09:26.720 --> 00:09:27.750 But remarkably,

NOTE Confidence: 0.874947232

00:09:27.750 --> 00:09:30.840 there is an increased risk of

NOTE Confidence: 0.874947232

00:09:30.840 --> 00:09:32.320 hepatocellular carcinoma even

NOTE Confidence: 0.874947232

00:09:32.320 --> 00:09:34.528 in non cirrhotic liver as well

NOTE Confidence: 0.874947232

00:09:34.528 --> 00:09:36.519 as renal cause renal cell.

NOTE Confidence: 0.874947232

00:09:36.520 --> 00:09:36.936 Arsenova,

NOTE Confidence: 0.874947232

00:09:36.936 --> 00:09:39.848 so this is a study being compiled

NOTE Confidence: 0.874947232

00:09:39.848 --> 00:09:42.650 with an international registry,

NOTE Confidence: 0.874947232

00:09:42.650 --> 00:09:45.050 but the foundational work for this

NOTE Confidence: 0.874947232

00:09:45.050 --> 00:09:47.665 study was laid at Yale in 2010,

NOTE Confidence: 0.874947232

00:09:47.665 --> 00:09:51.220 and this was a study that was led by

NOTE Confidence: 0.874947232

00:09:51.315 --> 00:09:54.625 Tamar Taddy and she looked at 406

NOTE Confidence: 0.874947232

00:09:54.625 --> 00:09:56.900 patients with Gaucher disease and

NOTE Confidence: 0.874947232

00:09:56.982 --> 00:10:00.402 found that overall cancer risk and

NOTE Confidence: 0.874947232

00:10:00.402 --> 00:10:02.682 demonstrate disease was increased,

NOTE Confidence: 0.874947232

00:10:02.690 --> 00:10:05.050 and particularly for multiple myeloma.

NOTE Confidence: 0.874947232

00:10:05.050 --> 00:10:06.170 Non hematologic.

NOTE Confidence: 0.874947232

00:10:06.170 --> 00:10:10.090 Answers and so this was the first

NOTE Confidence: 0.874947232

00:10:10.090 --> 00:10:12.766 demonstration of potential role
NOTE Confidence: 0.874947232

00:10:12.766 --> 00:10:15.462 of toxic glucosylceramide single
NOTE Confidence: 0.874947232

00:10:15.462 --> 00:10:17.484 lipids and carcinogenesis.
NOTE Confidence: 0.874947232

00:10:17.490 --> 00:10:17.969 Moreover,
NOTE Confidence: 0.874947232

00:10:17.969 --> 00:10:20.364 what tomorrow showed was that
NOTE Confidence: 0.874947232

00:10:20.364 --> 00:10:22.983 when she compiled Kaplan Meyer
NOTE Confidence: 0.874947232

00:10:22.983 --> 00:10:25.495 curves for polyclonal dermopathy
NOTE Confidence: 0.874947232

00:10:25.495 --> 00:10:28.007 monoclonal dermopathy of unknown
NOTE Confidence: 0.874947232

00:10:28.007 --> 00:10:30.290 significance and multiple myeloma,
NOTE Confidence: 0.874947232

00:10:30.290 --> 00:10:33.968 it immediately tells you that this
NOTE Confidence: 0.874947232

00:10:33.968 --> 00:10:37.037 lipid laden activated macrophages are
NOTE Confidence: 0.874947232

00:10:37.037 --> 00:10:40.052 talking to be lymphocytes and this
NOTE Confidence: 0.874947232

00:10:40.052 --> 00:10:43.279 led to a series of insightful studies
NOTE Confidence: 0.874947232

00:10:43.279 --> 00:10:46.470 by my colleague and lab member,
NOTE Confidence: 0.874947232

00:10:46.470 --> 00:10:47.612 Shiny Nair.
NOTE Confidence: 0.874947232

00:10:47.612 --> 00:10:51.038 Once it is long term question,

NOTE Confidence: 0.874947232

00:10:51.040 --> 00:10:53.266 which is that you can have

NOTE Confidence: 0.874947232

00:10:53.266 --> 00:10:54.750 massive splenomegaly in patients

NOTE Confidence: 0.874947232

00:10:54.818 --> 00:10:56.138 with calcium disease.

NOTE Confidence: 0.874947232

00:10:56.140 --> 00:10:59.317 And yet if you analyze the amount of lipids,

NOTE Confidence: 0.874947232

00:10:59.320 --> 00:11:02.959 it is barely 2% by weight and so the

NOTE Confidence: 0.874947232

00:11:02.959 --> 00:11:06.580 question is what is going on once the

NOTE Confidence: 0.874947232

00:11:06.580 --> 00:11:09.580 glucosylceramide lipids are accumulating?

NOTE Confidence: 0.874947232

00:11:09.580 --> 00:11:13.535 And what Chinese showed is that the

NOTE Confidence: 0.874947232

00:11:13.535 --> 00:11:16.177 macrophages are presenting the lipids

NOTE Confidence: 0.874947232

00:11:16.177 --> 00:11:19.639 in the context of CD1 molecules.

NOTE Confidence: 0.874947232

00:11:19.640 --> 00:11:20.696 And yeah,

NOTE Confidence: 0.874947232

00:11:20.696 --> 00:11:24.392 recognized by T cell receptors on a

NOTE Confidence: 0.874947232

00:11:24.392 --> 00:11:28.380 specific sub top subtype of NKT cells

NOTE Confidence: 0.874947232

00:11:28.380 --> 00:11:31.440 that harbor follicular helper phenotype.

NOTE Confidence: 0.874947232

00:11:31.440 --> 00:11:34.782 And this interaction leads to activation

NOTE Confidence: 0.874947232

00:11:34.782 --> 00:11:37.735 of germinal Center B lymphocytes
NOTE Confidence: 0.874947232

00:11:37.735 --> 00:11:40.860 and production of anti lipid,
NOTE Confidence: 0.874947232

00:11:40.860 --> 00:11:43.156 lipid reactive antibodies and
NOTE Confidence: 0.874947232

00:11:43.156 --> 00:11:46.026 if this process continues it
NOTE Confidence: 0.874947232

00:11:46.026 --> 00:11:48.578 eventually leads to gammopathy
NOTE Confidence: 0.874947232

00:11:48.578 --> 00:11:51.098 and multiple myeloma development.
NOTE Confidence: 0.874947232

00:11:51.100 --> 00:11:54.360 The lipid laden macrophages.
NOTE Confidence: 0.874947232

00:11:54.360 --> 00:11:56.244 Very interesting because there
NOTE Confidence: 0.874947232

00:11:56.244 --> 00:11:59.070 are a number of biomarkers that
NOTE Confidence: 0.874947232

00:11:59.151 --> 00:12:01.659 one can use in clinical practice,
NOTE Confidence: 0.874947232

00:12:01.660 --> 00:12:04.360 listed here, but also they.
NOTE Confidence: 0.874947232

00:12:04.360 --> 00:12:06.260 They expressed macrophage mannose
NOTE Confidence: 0.874947232

00:12:06.260 --> 00:12:09.110 receptor which is a way to
NOTE Confidence: 0.74931618

00:12:09.192 --> 00:12:12.293 get hold of you take enzyme molecules
NOTE Confidence: 0.74931618

00:12:12.293 --> 00:12:15.369 into the lysosomes of these macrophages.
NOTE Confidence: 0.74931618

00:12:15.370 --> 00:12:18.775 This concept has been advanced

NOTE Confidence: 0.74931618

00:12:18.775 --> 00:12:23.070 by showing that in fact these.

NOTE Confidence: 0.74931618

00:12:23.070 --> 00:12:26.395 Anti lipid antibodies can activate

NOTE Confidence: 0.74931618

00:12:26.395 --> 00:12:29.865 the complement and the C 5A so

NOTE Confidence: 0.74931618

00:12:29.865 --> 00:12:33.330 generated binds with the C 5A receptor,

NOTE Confidence: 0.74931618

00:12:33.330 --> 00:12:36.570 and paradoxically it increases the

NOTE Confidence: 0.74931618

00:12:36.570 --> 00:12:39.162 production of glucosylceramide synthase,

NOTE Confidence: 0.74931618

00:12:39.170 --> 00:12:41.130 making more of the lipids.

NOTE Confidence: 0.74931618

00:12:41.130 --> 00:12:44.084 So here we have an enzyme deficiency,

NOTE Confidence: 0.74931618

00:12:44.090 --> 00:12:46.430 and paradoxically this inflammatory

NOTE Confidence: 0.74931618

00:12:46.430 --> 00:12:49.940 pathway is leading to greater production

NOTE Confidence: 0.74931618

00:12:50.018 --> 00:12:53.014 of the lipid or positive feedback loop.

NOTE Confidence: 0.74931618

00:12:53.020 --> 00:12:56.899 And and this has led to a novel therapeutic

NOTE Confidence: 0.74931618

00:12:56.899 --> 00:12:59.685 target inhibitor of glucosylceramide

NOTE Confidence: 0.74931618

00:12:59.685 --> 00:13:03.460 centers which underwent clinical trials,

NOTE Confidence: 0.74931618

00:13:03.460 --> 00:13:07.820 and we were the principal center in a

NOTE Confidence: 0.74931618

00:13:07.820 --> 00:13:11.256 multi multinational study and it is now
NOTE Confidence: 0.74931618

00:13:11.256 --> 00:13:14.850 an approved drug with broad implications.
NOTE Confidence: 0.811952576

00:13:17.750 --> 00:13:20.918 And so this pathway has clearly
NOTE Confidence: 0.811952576

00:13:20.918 --> 00:13:23.030 relevance to common disease.
NOTE Confidence: 0.811952576

00:13:23.030 --> 00:13:26.964 So here shiny working with the mother
NOTE Confidence: 0.811952576

00:13:26.970 --> 00:13:31.116 showed that about 1/3 of sporadic
NOTE Confidence: 0.811952576

00:13:31.116 --> 00:13:34.382 multiple myeloma patients have their
NOTE Confidence: 0.811952576

00:13:34.382 --> 00:13:37.394 paraprotein that reacts to that shame.
NOTE Confidence: 0.811952576

00:13:37.400 --> 00:13:39.228 Lipids. Not only that,
NOTE Confidence: 0.811952576

00:13:39.228 --> 00:13:41.970 it reacts to another Lysol lipid
NOTE Confidence: 0.811952576

00:13:42.054 --> 00:13:44.630 called lysophosphatidylcholine,
NOTE Confidence: 0.811952576

00:13:44.630 --> 00:13:46.175 which we believe.
NOTE Confidence: 0.811952576

00:13:46.175 --> 00:13:50.400 He's a player in fatty liver disease,
NOTE Confidence: 0.811952576

00:13:50.400 --> 00:13:51.840 and interestingly,
NOTE Confidence: 0.811952576

00:13:51.840 --> 00:13:53.884 the genetic stratification of
NOTE Confidence: 0.811952576

00:13:53.884 --> 00:13:56.439 this lipid reactive come up.

NOTE Confidence: 0.811952576
00:13:56.440 --> 00:13:59.776 They showed that there were chromosome
NOTE Confidence: 0.811952576
00:13:59.780 --> 00:14:01.716 1Q21 abnormalities that were
NOTE Confidence: 0.811952576
00:14:01.716 --> 00:14:04.136 enriched in this patient population,
NOTE Confidence: 0.811952576
00:14:04.140 --> 00:14:06.870 and this is the locals
NOTE Confidence: 0.811952576
00:14:06.870 --> 00:14:09.600 that harbors the GBA gene.
NOTE Confidence: 0.811952576
00:14:09.600 --> 00:14:12.180 So this is the pathway that
NOTE Confidence: 0.811952576
00:14:12.180 --> 00:14:15.848 we've delineated in the Golgi
NOTE Confidence: 0.811952576
00:14:15.848 --> 00:14:17.720 glucosylceramide synthase.
NOTE Confidence: 0.811952576
00:14:17.720 --> 00:14:20.045 Activity leads to production of
NOTE Confidence: 0.811952576
00:14:20.045 --> 00:14:22.370 glucosylceramide and in the lysosome.
NOTE Confidence: 0.811952576
00:14:22.370 --> 00:14:25.538 This lipid is turned over and
NOTE Confidence: 0.811952576
00:14:25.538 --> 00:14:27.122 we went glucosylceramide.
NOTE Confidence: 0.811952576
00:14:27.130 --> 00:14:29.446 Cerebral side is sufficient.
NOTE Confidence: 0.811952576
00:14:29.446 --> 00:14:31.762 It activates an alternative
NOTE Confidence: 0.811952576
00:14:31.762 --> 00:14:34.387 pathway to get rid of this,
NOTE Confidence: 0.811952576

00:14:34.390 --> 00:14:36.895 accumulating lipid via the enzyme
NOTE Confidence: 0.811952576

00:14:36.895 --> 00:14:40.051 and said ceramic days to produce
NOTE Confidence: 0.811952576

00:14:40.051 --> 00:14:42.295 glucosides sphingosine and that
NOTE Confidence: 0.811952576

00:14:42.295 --> 00:14:45.655 allows the cell to export this
NOTE Confidence: 0.811952576

00:14:45.655 --> 00:14:47.960 lipid out of the cytoplasm.
NOTE Confidence: 0.811952576

00:14:47.960 --> 00:14:51.418 And at least advocate the cellular toxicity,
NOTE Confidence: 0.811952576

00:14:51.420 --> 00:14:54.978 but it causes other downstream problems.
NOTE Confidence: 0.811952576

00:14:54.980 --> 00:14:58.454 These lipids are cumulating are very
NOTE Confidence: 0.811952576

00:14:58.454 --> 00:15:00.770 potent inflammatory molecules as
NOTE Confidence: 0.811952576

00:15:00.862 --> 00:15:03.832 ligands for the MINKEL receptor and
NOTE Confidence: 0.811952576

00:15:03.832 --> 00:15:06.660 it generates anti lipid antibody.
NOTE Confidence: 0.811952576

00:15:06.660 --> 00:15:10.041 As I showed you and this downstream
NOTE Confidence: 0.811952576

00:15:10.041 --> 00:15:13.030 lipid has extreme potency as a
NOTE Confidence: 0.811952576

00:15:13.030 --> 00:15:15.445 bio active lipid and actually
NOTE Confidence: 0.811952576

00:15:15.445 --> 00:15:18.687 mediates a lot of the pathological.
NOTE Confidence: 0.811952576

00:15:18.690 --> 00:15:20.654 Manifestations of God, shade,

NOTE Confidence: 0.811952576
00:15:20.654 --> 00:15:21.636 disease and,
NOTE Confidence: 0.811952576
00:15:21.640 --> 00:15:22.034 importantly,
NOTE Confidence: 0.811952576
00:15:22.034 --> 00:15:25.580 the event on to validate this as a serum
NOTE Confidence: 0.811952576
00:15:25.656 --> 00:15:28.624 biomarker to be used in clinical trials,
NOTE Confidence: 0.811952576
00:15:28.630 --> 00:15:32.200 and this is one example in the
NOTE Confidence: 0.811952576
00:15:32.200 --> 00:15:34.806 Phase 2/3 clinical trials that
NOTE Confidence: 0.811952576
00:15:34.806 --> 00:15:37.950 they conducted where you are seeing
NOTE Confidence: 0.811952576
00:15:38.045 --> 00:15:40.885 biomarker responses to inhibitor
NOTE Confidence: 0.811952576
00:15:40.885 --> 00:15:43.725 of glucosylceramide synthase and
NOTE Confidence: 0.811952576
00:15:43.730 --> 00:15:46.824 what it shows is a Gaussian lipids,
NOTE Confidence: 0.811952576
00:15:46.830 --> 00:15:48.790 GL1 and lyso GL.
NOTE Confidence: 0.811952576
00:15:48.790 --> 00:15:50.260 Prasad single saying,
NOTE Confidence: 0.811952576
00:15:50.260 --> 00:15:52.976 have dramatically reduced and
NOTE Confidence: 0.811952576
00:15:52.976 --> 00:15:55.692 this marker of alternatively
NOTE Confidence: 0.811952576
00:15:55.692 --> 00:15:57.861 activated macrophage cytotoxicity
NOTE Confidence: 0.811952576

00:15:57.861 --> 00:16:00.749 days is concurrently reduced,
NOTE Confidence: 0.811952576

00:16:00.750 --> 00:16:04.230 as is a chemokine CCL 18 which is
NOTE Confidence: 0.811952576

00:16:04.230 --> 00:16:08.283 involved in T cell and B cell recruitment
NOTE Confidence: 0.811952576

00:16:08.283 --> 00:16:12.080 to liquidate an antigen presenting cells.
NOTE Confidence: 0.811952576

00:16:12.080 --> 00:16:15.360 So one of the central.
NOTE Confidence: 0.811952576

00:16:15.360 --> 00:16:18.769 A problem in Goshen disease management is,
NOTE Confidence: 0.811952576

00:16:18.770 --> 00:16:19.726 you know,
NOTE Confidence: 0.811952576

00:16:19.726 --> 00:16:20.682 topic diversity.
NOTE Confidence: 0.811952576

00:16:20.682 --> 00:16:23.072 There was great expectation that
NOTE Confidence: 0.811952576

00:16:23.072 --> 00:16:25.717 when you found once you found
NOTE Confidence: 0.811952576

00:16:25.717 --> 00:16:27.807 the genotype of Gaucher disease
NOTE Confidence: 0.811952576

00:16:27.886 --> 00:16:30.184 mutations then we will be able
NOTE Confidence: 0.811952576

00:16:30.184 --> 00:16:31.938 to predict prognosis accurately.
NOTE Confidence: 0.811952576

00:16:31.938 --> 00:16:34.902 This is the most common genotype
NOTE Confidence: 0.811952576

00:16:34.902 --> 00:16:37.627 in New York metropolitan area and
NOTE Confidence: 0.811952576

00:16:37.627 --> 00:16:40.659 you can see here the the onset

NOTE Confidence: 0.811952576
00:16:40.659 --> 00:16:42.539 of clinical manifestation can
NOTE Confidence: 0.811952576
00:16:42.539 --> 00:16:45.343 be in childhood and my oldest.
NOTE Confidence: 0.811952576
00:16:45.343 --> 00:16:48.061 Conditions are in their 70s or
NOTE Confidence: 0.811952576
00:16:48.061 --> 00:16:51.427 even 80s and you get the same
NOTE Confidence: 0.811952576
00:16:51.427 --> 00:16:53.343 kind of phenotypic diversity
NOTE Confidence: 0.811952576
00:16:53.343 --> 00:16:55.820 in other genotype groups.
NOTE Confidence: 0.811952576
00:16:55.820 --> 00:16:59.012 Although that is an overall true
NOTE Confidence: 0.811952576
00:16:59.012 --> 00:17:01.709 correlation such that this is
NOTE Confidence: 0.811952576
00:17:01.709 --> 00:17:04.054 the mildest phenotype and this
NOTE Confidence: 0.811952576
00:17:04.054 --> 00:17:06.930 is the most severe phenotype.
NOTE Confidence: 0.811952576
00:17:06.930 --> 00:17:09.709 So our goal has been to discover
NOTE Confidence: 0.811952576
00:17:09.709 --> 00:17:10.900 the modified genes,
NOTE Confidence: 0.811952576
00:17:10.900 --> 00:17:13.270 and I'm sure you've heard from
NOTE Confidence: 0.811952576
00:17:13.270 --> 00:17:15.670 workers in many other fields that
NOTE Confidence: 0.811952576
00:17:15.670 --> 00:17:18.557 this is has been the Holy Grail.
NOTE Confidence: 0.811952576

00:17:18.560 --> 00:17:21.836 And we decided to do a China
NOTE Confidence: 0.811952576

00:17:21.836 --> 00:17:23.240 Wide Association study,
NOTE Confidence: 0.811952576

00:17:23.240 --> 00:17:25.316 thinking that if we just selected
NOTE Confidence: 0.811952576

00:17:25.316 --> 00:17:28.359 the N 370 as homicidal statements,
NOTE Confidence: 0.811952576

00:17:28.360 --> 00:17:31.466 which are all Ashkenazi Jewish,
NOTE Confidence: 0.811952576

00:17:31.466 --> 00:17:34.004 and they have a founder mutation
NOTE Confidence: 0.811952576

00:17:34.004 --> 00:17:36.426 from 10th century that there are
NOTE Confidence: 0.811952576

00:17:36.426 --> 00:17:38.670 regions in the genome that are
NOTE Confidence: 0.760861613190476

00:17:38.745 --> 00:17:41.958 shared, and we may throw up a
NOTE Confidence: 0.760861613190476

00:17:41.958 --> 00:17:46.160 candidate modifier gene. And I'm sorry
NOTE Confidence: 0.766665435

00:17:46.160 --> 00:17:48.080 it's 236 we got we're running
NOTE Confidence: 0.766665435

00:17:48.080 --> 00:17:49.360 over so. To wrap it up,
NOTE Confidence: 0.812725810714286

00:17:49.670 --> 00:17:52.902 OK, so if I'm going to wrap this
NOTE Confidence: 0.812725810714286

00:17:52.902 --> 00:17:55.687 up after the next slide and.
NOTE Confidence: 0.812725810714286

00:17:55.690 --> 00:18:01.410 And we found a signal on a lipid sensor.
NOTE Confidence: 0.812725810714286

00:18:01.410 --> 00:18:05.730 Genes, CNA and this will be my last slide,

NOTE Confidence: 0.812725810714286
00:18:05.730 --> 00:18:08.898 so we were semble the largest
NOTE Confidence: 0.812725810714286
00:18:08.898 --> 00:18:11.684 cohort ever of 580 patients.
NOTE Confidence: 0.812725810714286
00:18:11.684 --> 00:18:13.475 International cohort to
NOTE Confidence: 0.812725810714286
00:18:13.475 --> 00:18:15.863 look at smart sequencing.
NOTE Confidence: 0.812725810714286
00:18:15.870 --> 00:18:18.354 Looking at this very gene dense
NOTE Confidence: 0.812725810714286
00:18:18.354 --> 00:18:20.670 region in the human genome.
NOTE Confidence: 0.812725810714286
00:18:20.670 --> 00:18:23.015 To look at this adjacent
NOTE Confidence: 0.812725810714286
00:18:23.015 --> 00:18:25.360 genes for modified genes in.
NOTE Confidence: 0.812725810714286
00:18:25.360 --> 00:18:28.916 I don't love the whole exome sequencing,
NOTE Confidence: 0.812725810714286
00:18:28.920 --> 00:18:31.080 so with that I will end and I
NOTE Confidence: 0.812725810714286
00:18:31.080 --> 00:18:32.700 apologize for going over time.
NOTE Confidence: 0.7708168503333333
00:18:34.020 --> 00:18:35.286 Thank you, Fran. That was great.