WEBVTT

00:00:00.000 --> 00:00:03.612 Hello everyone, I'd like to welcome

00:00:03.612 --> 00:00:07.574 everyone to the 2022 O'Brien Kidney

00:00:07.574 --> 00:00:11.164 Center at Yale Research Symposium.

00:00:11.170 --> 00:00:12.834 Advances in kidney research.

00:00:12.834 --> 00:00:15.807 Very grateful to shoot a Shelby for

00:00:15.807 --> 00:00:17.817 organizing this with antibodies help

00:00:17.817 --> 00:00:20.644 and thank you all for coming in

00:00:20.644 --> 00:00:22.930 attendance and and thank the speakers

00:00:22.930 --> 00:00:25.994 who are here and and speakers who will

00:00:25.994 --> 00:00:27.770 participate virtually for wonderful

00:00:27.770 --> 00:00:30.295 symposium that SHOOTED has organized.

00:00:30.300 --> 00:00:31.548 I want to say a couple of words.

00:00:31.550 --> 00:00:34.476 About what our O'Brien Center is about.

00:00:34.480 --> 00:00:36.185 Because there are services that

NOTE Confidence: 0.807361907222222

00:00:36.185 --> 00:00:38.301 might be useful to members of

NOTE Confidence: 0.807361907222222

00:00:38.301 --> 00:00:40.089 the kidney community, so let me.

NOTE Confidence: 0.74927117975

00:00:43.350 --> 00:00:46.241 The NDK has several kinds of research

NOTE Confidence: 0.74927117975

00:00:46.241 --> 00:00:48.859 centers of these research centers.

NOTE Confidence: 0.74927117975

00:00:48.860 --> 00:00:50.666 The O'Brien kidney centers are picked up,

NOTE Confidence: 0.74927117975

00:00:50.670 --> 00:00:54.018 particular subcategory and and these really

NOTE Confidence: 0.74927117975

00:00:54.018 --> 00:00:57.809 provide core services to aid investigators.

NOTE Confidence: 0.74927117975

00:00:57.810 --> 00:00:58.965 There's eight O'Brien

NOTE Confidence: 0.74927117975

00:00:58.965 --> 00:01:00.505 centers around the country.

NOTE Confidence: 0.74927117975

00:01:00.510 --> 00:01:02.491 These are not not not not have

NOTE Confidence: 0.74927117975

00:01:02.491 --> 00:01:04.278 major research grants that the major

NOTE Confidence: 0.74927117975

00:01:04.278 --> 00:01:06.042 mission of these is to support

NOTE Confidence: 0.74927117975

00:01:06.042 --> 00:01:07.858 research by providing core services,

NOTE Confidence: 0.74927117975

00:01:07.860 --> 00:01:10.600 they also have pilot grant

NOTE Confidence: 0.74927117975

00:01:10.600 --> 00:01:12.244 programs including ours.

NOTE Confidence: 0.74927117975

00:01:12.250 --> 00:01:13.780 The organization of our particular.

NOTE Confidence: 0.74927117975

00:01:13.780 --> 00:01:16.468 Center is shown here.

NOTE Confidence: 0.74927117975

00:01:16.470 --> 00:01:19.790 The we have three main cores that

NOTE Confidence: 0.74927117975

00:01:19.790 --> 00:01:21.740 provide different types of services,

NOTE Confidence: 0.74927117975

00:01:21.740 --> 00:01:24.148 but they kind of integrate to study kidney

NOTE Confidence: 0.74927117975

00:01:24.148 --> 00:01:26.740 disease at different levels of investigation.

NOTE Confidence: 0.74927117975

00:01:26.740 --> 00:01:28.625 We have an animal Physiology

NOTE Confidence: 0.74927117975

00:01:28.625 --> 00:01:29.756 and phenotyping core.

NOTE Confidence: 0.74927117975

00:01:29.760 --> 00:01:32.776 This led by Pat Price big that does

NOTE Confidence: 0.74927117975

00:01:32.776 --> 00:01:34.151 measurements different physiological

NOTE Confidence: 0.74927117975

00:01:34.151 --> 00:01:36.339 categories on small animals,

NOTE Confidence: 0.74927117975

00:01:36.340 --> 00:01:37.126 mainly mice.

NOTE Confidence: 0.74927117975

00:01:37.126 --> 00:01:39.484 We have a disease models and

NOTE Confidence: 0.74927117975

00:01:39.484 --> 00:01:41.373 mechanisms core that generates a

NOTE Confidence: 0.74927117975

00:01:41.373 --> 00:01:43.781 mouse and and cell line models of

NOTE Confidence: 0.74927117975

3

00:01:43.859 --> 00:01:46.478 disease and then we have a really a a.

00:01:46.480 --> 00:01:47.234 Complex core,

00:01:47.234 --> 00:01:49.119 the Human Genetics and clinical

00:01:49.119 --> 00:01:50.769 research core that provides

00:01:50.769 --> 00:01:52.577 resources for genetic studies

00:01:52.577 --> 00:01:54.385 and clinical research studies,

00:01:54.390 --> 00:01:57.970 biomarker assays, kidney injury studies,

00:01:57.970 --> 00:01:59.422 and I'll say more about the

00:01:59.422 --> 00:02:00.390 services in a minute.

00:02:03.580 --> 00:02:06.150 So the animal Physiology and

00:02:06.150 --> 00:02:08.320 phenotyping core provides a range

00:02:08.320 --> 00:02:10.600 of services that are listed here.

00:02:10.600 --> 00:02:13.220 GFR measurements and small

00:02:13.220 --> 00:02:15.840 animals mice profusion fixation.

00:02:15.840 --> 00:02:18.486 Essentially, a chemistry lab for measuring

00:02:18.486 --> 00:02:21.180 relevant serum and urine electrolytes,

00:02:21.180 --> 00:02:22.548 and creatinine. Blood,

00:02:22.548 --> 00:02:24.668 gas parameters, balance studies,

00:02:24.668 --> 00:02:26.480 circadian rhythm studies.

00:02:26.480 --> 00:02:28.444 Blood pressure measurements both

00:02:28.444 --> 00:02:31.390 in anesthetized mice and in awake

00:02:31.472 --> 00:02:33.260 mice by radio telemetry.

00:02:33.260 --> 00:02:35.255 Of the disease models and mechanisms core,

00:02:35.260 --> 00:02:36.618 which is led by Steve somehow and,

00:02:36.620 --> 00:02:37.492 like Cantley,

00:02:37.492 --> 00:02:39.672 provides access to unique mouse

00:02:39.672 --> 00:02:42.129 models and cell line resources.

00:02:42.130 --> 00:02:44.566 And it includes bacterial

00:02:44.566 --> 00:02:46.393 artificial chromosome transgenesis

00:02:46.393 --> 00:02:49.269 the support for CRISPR cast.

00:02:49.270 --> 00:02:51.670 You know, I'm editing support support

00:02:51.670 --> 00:02:54.100 for kidney cell line production.

NOTE Confidence: 0.765896327142857

00:02:54.100 --> 00:02:56.152 Performance of kidney ischemia,

NOTE Confidence: 0.765896327142857

00:02:56.152 --> 00:02:57.178 reperfusion surgery,

NOTE Confidence: 0.765896327142857

00:02:57.180 --> 00:02:59.118 and support for development of imaging,

NOTE Confidence: 0.765896327142857

00:02:59.120 --> 00:03:00.368 mass cytometry,

NOTE Confidence: 0.765896327142857

00:03:00.368 --> 00:03:03.488 and human kidney biopsy samples.

NOTE Confidence: 0.765896327142857

00:03:03.490 --> 00:03:05.212 And then finally,

NOTE Confidence: 0.765896327142857

00:03:05.212 --> 00:03:06.360 there's the.

NOTE Confidence: 0.765896327142857

00:03:06.360 --> 00:03:08.280 Genetics and clinical research

NOTE Confidence: 0.765896327142857

00:03:08.280 --> 00:03:10.484 for that has multiple directors

NOTE Confidence: 0.765896327142857

00:03:10.484 --> 00:03:11.777 overseeing different components.

NOTE Confidence: 0.765896327142857

00:03:11.780 --> 00:03:14.180 Perry Wilson, Srikant Mani and Steve.

NOTE Confidence: 0.765896327142857

00:03:14.180 --> 00:03:16.637 Somehow here at Yale and Chirag Parikh

NOTE Confidence: 0.765896327142857

00:03:16.637 --> 00:03:18.699 overseeing the component of Johns Hopkins,

NOTE Confidence: 0.765896327142857

00:03:18.700 --> 00:03:20.986 and this provides services to enhance

NOTE Confidence: 0.765896327142857

00:03:20.986 --> 00:03:22.510 different aspects of translational

NOTE Confidence: 0.765896327142857

00:03:22.569 --> 00:03:23.997 studies and kidney disease,

NOTE Confidence: 0.765896327142857

00:03:24.000 --> 00:03:25.990 the genetics and genomic studies

NOTE Confidence: 0.765896327142857

00:03:25.990 --> 00:03:27.980 include DNA extraction and archiving,

NOTE Confidence: 0.765896327142857

00:03:27.980 --> 00:03:31.444 snip genotyping, exome sequencing,

NOTE Confidence: 0.765896327142857

00:03:31.444 --> 00:03:33.176 transcriptome analysis,

NOTE Confidence: 0.765896327142857

00:03:33.180 --> 00:03:34.863 and bioinformatics support.

NOTE Confidence: 0.765896327142857

00:03:34.863 --> 00:03:36.546 Clinical Research Services.

NOTE Confidence: 0.765896327142857

00:03:36.550 --> 00:03:37.966 Through protocol development,

NOTE Confidence: 0.765896327142857

00:03:37.966 --> 00:03:40.326 patient recruitment and sample processing,

NOTE Confidence: 0.765896327142857

00:03:40.330 --> 00:03:42.805 bio and data banking archive

NOTE Confidence: 0.765896327142857

00:03:42.805 --> 00:03:44.785 samples from NIH studies.

NOTE Confidence: 0.765896327142857

00:03:44.790 --> 00:03:47.020 Many types of biomarker assays,

NOTE Confidence: 0.765896327142857

00:03:47.020 --> 00:03:49.050 and importantly and most recently,

NOTE Confidence: 0.765896327142857

00:03:49.050 --> 00:03:50.196 extraction analysis of

NOTE Confidence: 0.765896327142857

00:03:50.196 --> 00:03:51.724 electronic health record data.

NOTE Confidence: 0.765896327142857

00:03:51.730 --> 00:03:53.950 Machine learning and biostatistical

NOTE Confidence: 0.765896327142857

00:03:53.950 --> 00:03:56.639 support and Perry Wilson provides

NOTE Confidence: 0.765896327142857

00:03:56.639 --> 00:03:58.984 a course on research methods

NOTE Confidence: 0.765896327142857

00:03:58.984 --> 00:04:00.391 and statistical interpretation

NOTE Confidence: 0.765896327142857

00:04:00.391 --> 00:04:02.099 that's available through Coursera

NOTE Confidence: 0.765896327142857

00:04:02.099 --> 00:04:04.433 and that can be found online.

NOTE Confidence: 0.892226405

00:04:06.570 --> 00:04:07.690 And we're very grateful

NOTE Confidence: 0.892226405

00:04:07.690 --> 00:04:08.810 to our External Board,

NOTE Confidence: 0.892226405

00:04:08.810 --> 00:04:10.910 the Chair Peter Igarashi has traveled

NOTE Confidence: 0.892226405

00:04:10.910 --> 00:04:13.129 here from Minnesota to attend today.

NOTE Confidence: 0.892226405

00:04:13.130 --> 00:04:15.242 The other members of the board of Laura

NOTE Confidence: 0.892226405

00:04:15.242 --> 00:04:17.227 Denver at Ali Garavi and Marco Cusa,

NOTE Confidence: 0.892226405

00:04:17.230 --> 00:04:19.710 and they provide a very important function in

NOTE Confidence: 0.892226405

00:04:19.710 --> 00:04:21.730 providing advice and guidance to the center,

NOTE Confidence: 0.892226405

00:04:21.730 --> 00:04:23.602 and also they provide the review

NOTE Confidence: 0.892226405

00:04:23.602 --> 00:04:25.400 of our pilot grant program.

NOTE Confidence: 0.892226405

00:04:25.400 --> 00:04:27.002 We recently had a deadline and

NOTE Confidence: 0.892226405

00:04:27.002 --> 00:04:28.881 the beginning of May and and these

NOTE Confidence: 0.892226405

00:04:28.881 --> 00:04:30.638 grants will be reviewed by by this

NOTE Confidence: 0.892226405

00:04:30.699 --> 00:04:32.404 group and we're very grateful

NOTE Confidence: 0.892226405

00:04:32.404 --> 00:04:33.768 for their participation and

NOTE Confidence: 0.892226405

00:04:33.768 --> 00:04:36.930 helping the center be successful.

NOTE Confidence: 0.892226405

00:04:36.930 --> 00:04:37.722 So with that,

NOTE Confidence: 0.892226405

00:04:37.722 --> 00:04:39.570 we'll get to the business that you're

NOTE Confidence: 0.892226405

00:04:39.631 --> 00:04:41.409 here for is to hear the wonderful

NOTE Confidence: 0.892226405

00:04:41.409 --> 00:04:43.100 talks that have been lined up by

NOTE Confidence: 0.892226405

00:04:43.100 --> 00:04:44.836 shutta and let me turn it over to

NOTE Confidence: 0.892226405

00:04:44.836 --> 00:04:46.114 Shruti to introduce our first speaker.

NOTE Confidence: 0.815431719166667

00:04:53.400 --> 00:04:55.044 It's great that we were able

NOTE Confidence: 0.815431719166667

00:04:55.044 --> 00:04:56.800 to do this online this year,

NOTE Confidence: 0.815431719166667

00:04:56.800 --> 00:04:58.627 and people who were able to join

NOTE Confidence: 0.815431719166667

00:04:58.627 --> 00:05:00.304 us physically as well as virtually

NOTE Confidence: 0.815431719166667

00:05:00.304 --> 00:05:01.972 for those who are joining us.

NOTE Confidence: 0.815431719166667

00:05:01.980 --> 00:05:04.135 Virtually. Please ask your questions

NOTE Confidence: 0.815431719166667

00:05:04.135 --> 00:05:06.805 by chat and I'll be visualizing

NOTE Confidence: 0.815431719166667

00:05:06.805 --> 00:05:09.836 it while I listen to these talks.

NOTE Confidence: 0.815431719166667

00:05:09.840 --> 00:05:12.776 So the first speaker will be doctor Jody

NOTE Confidence: 0.815431719166667

00:05:12.776 --> 00:05:15.178 Babbitt from Harvard Medical School,

NOTE Confidence: 0.815431719166667

00:05:15.180 --> 00:05:17.616 and she'll be talking to us

NOTE Confidence: 0.815431719166667

00:05:17.616 --> 00:05:19.240 about systemic iron homeostasis,

NOTE Confidence: 0.815431719166667

00:05:19.240 --> 00:05:20.884 translating molecular discoveries

NOTE Confidence: 0.815431719166667

00:05:20.884 --> 00:05:23.624 to chronic kidney disease patients.

NOTE Confidence: 0.815431719166667

00:05:23.630 --> 00:05:24.110 Thank you.

NOTE Confidence: 0.916836806666667

00:05:51.160 --> 00:05:53.356 Great thank you for that kind

NOTE Confidence: 0.916836806666667

00:05:53.356 --> 00:05:55.603 introduction and I thank you for

NOTE Confidence: 0.916836806666667

00:05:55.603 --> 00:05:57.739 the opportunity to speak with you.

NOTE Confidence: 0.916836806666667

00:05:57.740 --> 00:05:59.400 Very exciting to finally be

NOTE Confidence: 0.916836806666667

00:05:59.400 --> 00:06:01.540 back at some in person meetings

NOTE Confidence: 0.916836806666667

00:06:01.540 --> 00:06:03.590 or hybrid meetings at least.

NOTE Confidence: 0.916836806666667

00:06:03.590 --> 00:06:05.390 So I'm going to talk to you today

NOTE Confidence: 0.916836806666667

00:06:05.390 --> 00:06:06.690 about systemic iron homeostasis,

NOTE Confidence: 0.916836806666667

00:06:06.690 --> 00:06:08.892 translating molecular discoveries,

NOTE Confidence: 0.916836806666667

00:06:08.892 --> 00:06:10.360 sophisticated patients

NOTE Confidence: 0.916836806666667

00:06:10.360 --> 00:06:13.180 disclosures are shown here.

NOTE Confidence: 0.916836806666667

00:06:13.180 --> 00:06:14.908 So the goals of this presentation

NOTE Confidence: 0.916836806666667

00:06:14.908 --> 00:06:16.419 are to understand the important

NOTE Confidence: 0.916836806666667

00:06:16.419 --> 00:06:18.255 role of iron in health disease.

NOTE Confidence: 0.916836806666667

00:06:18.260 --> 00:06:20.199 To understand the central role of the

NOTE Confidence: 0.916836806666667

00:06:20.199 --> 00:06:22.103 upside and Fairport and access and

NOTE Confidence: 0.916836806666667

00:06:22.103 --> 00:06:23.803 systemic iron homeostasis regulation and

NOTE Confidence: 0.916836806666667

00:06:23.803 --> 00:06:25.558 iron disorders including the anemia,

NOTE Confidence: 0.916836806666667

00:06:25.560 --> 00:06:26.688 afrinic kidney disease.

NOTE Confidence: 0.916836806666667

00:06:26.688 --> 00:06:28.568 Do you understand the molecular

NOTE Confidence: 0.916836806666667

00:06:28.568 --> 00:06:30.476 regulation of hepcidin and how

NOTE Confidence: 0.916836806666667

00:06:30.476 --> 00:06:32.301 abnormalities in these pathways contribute

NOTE Confidence: 0.916836806666667

00:06:32.301 --> 00:06:34.837 to iron disorders and to discuss

NOTE Confidence: 0.916836806666667

00:06:34.837 --> 00:06:36.145 potential translational applications

NOTE Confidence: 0.916836806666667

00:06:36.145 --> 00:06:39.450 of these molecular discoveries?

NOTE Confidence: 0.916836806666667

00:06:39.450 --> 00:06:40.890 So as I'm sure I don't need to

NOTE Confidence: 0.916836806666667

00:06:40.890 --> 00:06:42.229 tell this audience anemia is

NOTE Confidence: 0.916836806666667

00:06:42.229 --> 00:06:43.779 prevalent in chronic kidney disease.

NOTE Confidence: 0.916836806666667

00:06:43.780 --> 00:06:45.593 This is data from CK Dopps showing

NOTE Confidence: 0.916836806666667

00:06:45.593 --> 00:06:47.304 that in countries across the world

NOTE Confidence: 0.916836806666667

00:06:47.304 --> 00:06:48.769 as patients reach stage three,

NOTE Confidence: 0.916836806666667

00:06:48.770 --> 00:06:52.706 CKD already about 50% of patients are anemic.

NOTE Confidence: 0.916836806666667

00:06:52.710 --> 00:06:55.846 This increases to 90% in stage five

NOTE Confidence: 0.916836806666667

00:06:55.846 --> 00:06:58.735 CKD and becoming almost universal

NOTE Confidence: 0.916836806666667

00:06:58.735 --> 00:07:00.910 in hemodialysis patients.

NOTE Confidence: 0.916836806666667

00:07:00.910 --> 00:07:02.665 Anemia and CKD is associated

NOTE Confidence: 0.916836806666667

00:07:02.665 --> 00:07:04.069 with numerous address outcomes,

NOTE Confidence: 0.916836806666667

00:07:04.070 --> 00:07:05.768 including a reduced quality of life,

NOTE Confidence: 0.916836806666667

00:07:05.770 --> 00:07:07.186 cardiovascular disease,

NOTE Confidence: 0.916836806666667

00:07:07.186 --> 00:07:09.310 hospitalizations, cognitive impairment,

NOTE Confidence: 0.916836806666667

00:07:09.310 --> 00:07:13.050 CKD progression, and mortality.

NOTE Confidence: 0.916836806666667

00:07:13.050 --> 00:07:16.178 And and this is illustrated in one such

NOTE Confidence: 0.916836806666667

00:07:16.178 --> 00:07:19.160 study here of of US male veterans showing

NOTE Confidence: 0.916836806666667

00:07:19.160 --> 00:07:22.058 that as patients become more anemic,

NOTE Confidence: 0.916836806666667

00:07:22.060 --> 00:07:23.615 there is an increasing risk

NOTE Confidence: 0.916836806666667

00:07:23.615 --> 00:07:25.900 of the end point of end stage,

NOTE Confidence: 0.916836806666667

00:07:25.900 --> 00:07:27.432 kidney disease or mortality.

NOTE Confidence: 0.916836806666667

00:07:27.432 --> 00:07:30.312 And this is still significant even after

NOTE Confidence: 0.916836806666667

00:07:30.312 --> 00:07:32.360 adjusting for potential confounders.

NOTE Confidence: 0.883932766470588

00:07:34.940 --> 00:07:36.782 Now there are two important ingredients

NOTE Confidence: 0.883932766470588

00:07:36.782 --> 00:07:38.719 in red cell production that are

NOTE Confidence: 0.883932766470588

00:07:38.719 --> 00:07:40.349 disturbed in kidney disease patients.

NOTE Confidence: 0.883932766470588

00:07:40.350 --> 00:07:41.490 One is the mythopoetic,

NOTE Confidence: 0.883932766470588

00:07:41.490 --> 00:07:43.595 the hormone made by the kidney that's

NOTE Confidence: 0.883932766470588

00:07:43.595 --> 00:07:45.623 important to induce the maturation of

NOTE Confidence: 0.883932766470588

00:07:45.623 --> 00:07:47.788 fluoridation of red cells from the precursors

NOTE Confidence: 0.883932766470588

00:07:47.788 --> 00:07:50.682 in the bone marrow and the 2nd is iron,

NOTE Confidence: 0.883932766470588

00:07:50.682 --> 00:07:53.580 which is an essential component of hemoglobin

NOTE Confidence: 0.883932766470588

00:07:53.652 --> 00:07:56.148 that allows it to transport oxygen.

NOTE Confidence: 0.883932766470588

00:07:56.150 --> 00:07:57.925 The problem with EPO is

NOTE Confidence: 0.883932766470588

00:07:57.925 --> 00:07:59.345 illustrated in this slide.

NOTE Confidence: 0.883932766470588

00:07:59.350 --> 00:08:00.782 So in patients without

NOTE Confidence: 0.883932766470588

00:08:00.782 --> 00:08:01.856 chronic kidney disease,

NOTE Confidence: 0.883932766470588

00:08:01.860 --> 00:08:03.650 as patients become more anemic,

NOTE Confidence: 0.883932766470588

00:08:03.650 --> 00:08:05.912 they're able to robustly induce the

NOTE Confidence: 0.883932766470588

00:08:05.912 --> 00:08:08.838 production of reports in which can help treat

NOTE Confidence: 0.883932766470588

00:08:08.838 --> 00:08:11.468 the reverse the anemia as CKD progresses,

NOTE Confidence: 0.883932766470588

00:08:11.468 --> 00:08:14.450 patients lose the ability for anemia to

NOTE Confidence: 0.883932766470588

00:08:14.531 --> 00:08:17.399 induce the production of earth portion,

NOTE Confidence: 0.883932766470588

00:08:17.400 --> 00:08:19.136 and this is one of the major causes

NOTE Confidence: 0.883932766470588

00:08:19.136 --> 00:08:20.928 of anemia and chronic kidney disease.

NOTE Confidence: 0.883932766470588

00:08:20.930 --> 00:08:21.680 And of course,

NOTE Confidence: 0.883932766470588

00:08:21.680 --> 00:08:24.118 this has led to the use of recombinant

NOTE Confidence: 0.883932766470588

00:08:24.118 --> 00:08:26.610 erythropoietin or other erythropoiesis.

NOTE Confidence: 0.883932766470588

00:08:26.610 --> 00:08:27.866 Stimulating agents which are

NOTE Confidence: 0.883932766470588

00:08:27.866 --> 00:08:29.436 a mainstay of anemia therapy,

NOTE Confidence: 0.883932766470588

00:08:29.440 --> 00:08:31.230 and these have really revolutionized

NOTE Confidence: 0.883932766470588

00:08:31.230 --> 00:08:33.481 anemia therapy and that they have

NOTE Confidence: 0.883932766470588

00:08:33.481 --> 00:08:35.863 improved quality of life and have

NOTE Confidence: 0.883932766470588

00:08:35.863 --> 00:08:37.054 reduced transfusion requirements.

NOTE Confidence: 0.883932766470588

00:08:37.060 --> 00:08:39.398 But they do not improve other adverse

NOTE Confidence: 0.883932766470588

00:08:39.398 --> 00:08:40.840 outcomes associated with anemia,

NOTE Confidence: 0.883932766470588

00:08:40.840 --> 00:08:42.469 including cardiovascular disease,

NOTE Confidence: 0.883932766470588

00:08:42.469 --> 00:08:44.098 hospitalization and mortality,

NOTE Confidence: 0.883932766470588

00:08:44.100 --> 00:08:45.930 and prospective randomized control trials.

NOTE Confidence: 0.8865048925

00:08:48.950 --> 00:08:52.718 Some of the key trials are listed here.

NOTE Confidence: 0.8865048925

00:08:52.720 --> 00:08:54.880 So, So what about iron?

NOTE Confidence: 0.8865048925

00:08:54.880 --> 00:08:57.560 So just as anemia is prevalent in CKD,

NOTE Confidence: 0.8865048925

00:08:57.560 --> 00:08:58.656 so is iron deficiency.

NOTE Confidence: 0.8865048925

00:08:58.656 --> 00:09:01.015 This is again data from CK Docs showing

NOTE Confidence: 0.8865048925

00:09:01.015 --> 00:09:02.965 that in countries across the world

NOTE Confidence: 0.8865048925

00:09:02.965 --> 00:09:05.018 and across different stages of CKD,

NOTE Confidence: 0.8865048925

00:09:05.020 --> 00:09:07.176 about 40 to 60% of patients have

NOTE Confidence: 0.8865048925

00:09:07.176 --> 00:09:09.269 some form of iron deficiency.

NOTE Confidence: 0.729874166857143

00:09:12.510 --> 00:09:13.605 With adverse outcomes,

NOTE Confidence: 0.729874166857143

00:09:13.605 --> 00:09:16.160 this is a data from a historical

NOTE Confidence: 0.729874166857143

00:09:16.229 --> 00:09:17.689 cohort of US veterans.

16

NOTE Confidence: 0.729874166857143

00:09:17.690 --> 00:09:18.929 Almost 33,000 patients,

NOTE Confidence: 0.729874166857143

00:09:18.929 --> 00:09:22.429 and what you can see is that patients

NOTE Confidence: 0.729874166857143

00:09:22.429 --> 00:09:25.573 in the lowest quartiles of transparent

NOTE Confidence: 0.729874166857143

00:09:25.573 --> 00:09:28.767 saturation that is below 16.6% had an

NOTE Confidence: 0.729874166857143

00:09:28.767 --> 00:09:31.041 increased risk of one year mortality

NOTE Confidence: 0.729874166857143

00:09:31.041 --> 00:09:33.210 compared to the reference group and

NOTE Confidence: 0.729874166857143

00:09:33.210 --> 00:09:35.450 and as is usual in the in biology,

NOTE Confidence: 0.729874166857143

00:09:35.450 --> 00:09:37.666 there where there are often J shaped curves,

NOTE Confidence: 0.729874166857143

00:09:37.670 --> 00:09:39.335 they even found that that

NOTE Confidence: 0.729874166857143

00:09:39.335 --> 00:09:40.667 patients in the highest.

NOTE Confidence: 0.729874166857143

00:09:40.670 --> 00:09:42.782 Modi also tended to have an

NOTE Confidence: 0.729874166857143

00:09:42.782 --> 00:09:44.376 increased risk of talented,

NOTE Confidence: 0.729874166857143

00:09:44.376 --> 00:09:45.448 quite rich.

NOTE Confidence: 0.909468342857143

00:09:47.460 --> 00:09:50.460 So in order to try to understand a little bit

NOTE Confidence: 0.909468342857143

00:09:50.531 --> 00:09:52.856 more about why iron deficiency may be bad,

NOTE Confidence: 0.909468342857143

17

00:09:52.856 --> 00:09:55.060 and perhaps too much iron may be harmful,

NOTE Confidence: 0.909468342857143

00:09:55.060 --> 00:09:56.691 it's helpful to know a little bit

NOTE Confidence: 0.909468342857143

00:09:56.691 --> 00:09:58.219 more about the biology of iron.

NOTE Confidence: 0.909468342857143

00:09:58.220 --> 00:10:00.900 So let's discuss that briefly.

NOTE Confidence: 0.909468342857143

00:10:00.900 --> 00:10:03.180 So iron is a transition metal.

NOTE Confidence: 0.909468342857143

00:10:03.180 --> 00:10:05.396 It's it's ability to be able to readily

NOTE Confidence: 0.909468342857143

00:10:05.396 --> 00:10:07.679 donate and accept electrons is what allows

NOTE Confidence: 0.909468342857143

00:10:07.679 --> 00:10:09.960 iron to perform its biologic functions.

NOTE Confidence: 0.909468342857143

00:10:09.960 --> 00:10:12.424 This allows iron to perform the most

NOTE Confidence: 0.909468342857143

00:10:12.424 --> 00:10:14.617 well known function as a component

NOTE Confidence: 0.909468342857143

00:10:14.617 --> 00:10:16.753 of heme and and transporting oxygen.

NOTE Confidence: 0.909468342857143

00:10:16.760 --> 00:10:18.458 But it's probably less well recognized

NOTE Confidence: 0.909468342857143

00:10:18.458 --> 00:10:19.920 and folks outside this field.

NOTE Confidence: 0.909468342857143

00:10:19.920 --> 00:10:21.738 It turns out that heme itself,

NOTE Confidence: 0.909468342857143

00:10:21.740 --> 00:10:23.384 as well as other iron functional

NOTE Confidence: 0.909468342857143

00:10:23.384 --> 00:10:25.380 groups such as iron sulfur crossers,

NOTE Confidence: 0.909468342857143

00:10:25.380 --> 00:10:27.192 are actually key components of a

NOTE Confidence: 0.909468342857143

00:10:27.192 --> 00:10:29.388 number of other proteins that perform

NOTE Confidence: 0.909468342857143

00:10:29.388 --> 00:10:30.786 fundamental cellular processes,

NOTE Confidence: 0.909468342857143

00:10:30.790 --> 00:10:33.502 and everything from the TCA cycle

NOTE Confidence: 0.909468342857143

00:10:33.502 --> 00:10:35.903 to electron transport to DNA

NOTE Confidence: 0.909468342857143

00:10:35.903 --> 00:10:38.438 synthesis and many other functions.

NOTE Confidence: 0.909468342857143

00:10:38.440 --> 00:10:41.528 And so iron really is essential for life.

NOTE Confidence: 0.909468342857143

00:10:41.530 --> 00:10:44.858 And iron deficiency can not only lead to

NOTE Confidence: 0.909468342857143

00:10:44.858 --> 00:10:47.978 anemia but also cardiovascular strain,

NOTE Confidence: 0.909468342857143

00:10:47.980 --> 00:10:49.555 impaired muscle function,

NOTE Confidence: 0.909468342857143

00:10:49.555 --> 00:10:52.180 exercise tolerance and work performance,

NOTE Confidence: 0.909468342857143

00:10:52.180 --> 00:10:53.916 altered immune function and

NOTE Confidence: 0.909468342857143

00:10:53.916 --> 00:10:55.218 increases in children.

NOTE Confidence: 0.909468342857143

00:10:55.220 --> 00:10:56.630 Developmental defects,

NOTE Confidence: 0.909468342857143

00:10:56.630 --> 00:11:00.155 growth retardation and neurologic defects.

NOTE Confidence: 0.909468342857143

00:11:00.160 --> 00:11:01.912 This property of iron that allows

NOTE Confidence: 0.909468342857143

00:11:01.912 --> 00:11:03.480 it to perform its biological

NOTE Confidence: 0.909468342857143

00:11:03.480 --> 00:11:05.538 functions also means that when an

NOTE Confidence: 0.909468342857143

00:11:05.538 --> 00:11:07.952 excess iron can participate in the

NOTE Confidence: 0.909468342857143

00:11:07.952 --> 00:11:09.716 so-called Fenton mediated reaction,

NOTE Confidence: 0.909468342857143

00:11:09.720 --> 00:11:11.827 which leads to the production of pre

NOTE Confidence: 0.909468342857143

00:11:11.827 --> 00:11:13.840 oxygen radicals that can damage proteins,

NOTE Confidence: 0.909468342857143

00:11:13.840 --> 00:11:16.580 lipids and nucleic acids.

NOTE Confidence: 0.909468342857143

00:11:16.580 --> 00:11:19.520 Leading to cellular damage and dysfunction,

NOTE Confidence: 0.909468342857143

00:11:19.520 --> 00:11:21.080 and the most clear clinical evidence

NOTE Confidence: 0.909468342857143

00:11:21.080 --> 00:11:22.885 of of the the adverse consequences

NOTE Confidence: 0.909468342857143

00:11:22.885 --> 00:11:25.009 of iron overload come from genetic

NOTE Confidence: 0.909468342857143

00:11:25.009 --> 00:11:26.499 disorders of iron overload,

NOTE Confidence: 0.909468342857143

00:11:26.500 --> 00:11:28.208 such as hereditary hemochromatosis,

NOTE Confidence: 0.909468342857143

00:11:28.208 --> 00:11:30.770 where excess iron deposits and organs,

NOTE Confidence: 0.909468342857143

00:11:30.770 --> 00:11:31.960 such as the liver, heart,

NOTE Confidence: 0.909468342857143

00:11:31.960 --> 00:11:33.202 and endocrine glands,

NOTE Confidence: 0.909468342857143

00:11:33.202 --> 00:11:34.858 leading to organ dysfunction.

NOTE Confidence: 0.909468342857143

00:11:34.860 --> 00:11:36.520 There's also another category of

NOTE Confidence: 0.909468342857143

00:11:36.520 --> 00:11:38.180 diseases called iron loading anemias,

NOTE Confidence: 0.909468342857143

00:11:38.180 --> 00:11:40.580 of which Felicia is a prototypical

NOTE Confidence: 0.909468342857143

00:11:40.580 --> 00:11:42.180 example in these disorders.

NOTE Confidence: 0.909468342857143

00:11:42.180 --> 00:11:43.820 Mutations in the protein components

NOTE Confidence: 0.909468342857143

00:11:43.820 --> 00:11:45.869 of hemoglobin and lead to ineffective

NOTE Confidence: 0.909468342857143

00:11:45.869 --> 00:11:47.619 with the poises and anemia.

NOTE Confidence: 0.909468342857143

00:11:47.620 --> 00:11:49.755 In more severe forms of these diseases,

NOTE Confidence: 0.909468342857143

00:11:49.760 --> 00:11:51.096 patients are transfusion dependent

NOTE Confidence: 0.909468342857143

00:11:51.096 --> 00:11:53.100 and can get secondary iron overload

NOTE Confidence: 0.909468342857143

00:11:53.150 --> 00:11:54.200 from the transfusions.

NOTE Confidence: 0.909468342857143

00:11:54.200 --> 00:11:55.544 But even in less severe forms

NOTE Confidence: 0.909468342857143

00:11:55.544 --> 00:11:56.216 of this disease,

NOTE Confidence: 0.909468342857143

00:11:56.220 --> 00:11:57.390 there's actually underlying

NOTE Confidence: 0.909468342857143

00:11:57.390 --> 00:11:59.340 pathophysiology in this disease that

NOTE Confidence: 0.909468342857143

00:11:59.340 --> 00:12:01.780 leads to dietary iron hyper absorption,

NOTE Confidence: 0.909468342857143

00:12:01.780 --> 00:12:03.880 which also contributes to iron overload,

NOTE Confidence: 0.909468342857143

00:12:03.880 --> 00:12:06.632 and iron overload is a major cause of

NOTE Confidence: 0.909468342857143

00:12:06.632 --> 00:12:09.219 morbidity and mortality in this disorder.

NOTE Confidence: 0.909468342857143

00:12:09.220 --> 00:12:09.566 Now,

NOTE Confidence: 0.909468342857143

00:12:09.566 --> 00:12:10.604 because you know,

NOTE Confidence: 0.909468342857143

00:12:10.604 --> 00:12:12.680 it turns out that even outside

NOTE Confidence: 0.909468342857143

00:12:12.746 --> 00:12:14.858 the massive iron overload that we

NOTE Confidence: 0.909468342857143

00:12:14.858 --> 00:12:16.990 see in these genetic disorders,

NOTE Confidence: 0.909468342857143

00:12:16.990 --> 00:12:18.796 there's also evidence in the literature

NOTE Confidence: 0.909468342857143

00:12:18.796 --> 00:12:20.944 that excess iron levels can also be

NOTE Confidence: 0.909468342857143

00:12:20.944 --> 00:12:22.434 associated with more common disorders.

NOTE Confidence: 0.909468342857143

00:12:22.440 --> 00:12:24.392 Everything from diabetes melodus

NOTE Confidence: 0.909468342857143

00:12:24.392 --> 00:12:25.856 to cardiovascular disease,

NOTE Confidence: 0.909468342857143

00:12:25.860 --> 00:12:28.040 neurogenic disorders, acute kidney injury,

NOTE Confidence: 0.909468342857143

00:12:28.040 --> 00:12:28.570 and malignancy,

NOTE Confidence: 0.909468342857143

00:12:28.570 --> 00:12:30.690 and just as all cells in our body

NOTE Confidence: 0.909468342857143

00:12:30.753 --> 00:12:32.378 need iron to grow proliferate.

NOTE Confidence: 0.909468342857143

00:12:32.380 --> 00:12:34.180 So do infectious organisms and and.

NOTE Confidence: 0.909468342857143

00:12:34.180 --> 00:12:35.644 And we know when and patients

NOTE Confidence: 0.909468342857143

00:12:35.644 --> 00:12:36.620 with iron overload disorders,

NOTE Confidence: 0.909468342857143

00:12:36.620 --> 00:12:38.726 that they're more prone to infection.

NOTE Confidence: 0.909468342857143

00:12:38.730 --> 00:12:40.454 Certain types of infections.

NOTE Confidence: 0.909468342857143

00:12:40.454 --> 00:12:43.040 For example Center for the bacteria.

NOTE Confidence: 0.909468342857143

00:12:43.040 --> 00:12:44.550 Now, because iron is essential,

NOTE Confidence: 0.909468342857143

00:12:44.550 --> 00:12:46.335 but too much iron can be toxic,

NOTE Confidence: 0.909468342857143

00:12:46.340 --> 00:12:48.706 iron levels must be very carefully regulated,

NOTE Confidence: 0.844118134285714

00:12:48.710 --> 00:12:51.594 both at the cellular level and systemically,

NOTE Confidence: 0.844118134285714

00:12:51.600 --> 00:12:52.500 and it's systemic.

NOTE Confidence: 0.844118134285714

00:12:52.500 --> 00:12:54.000 Own homemade stasis that we're

00:12:54.000 --> 00:12:55.538 going to talk about today.

00:12:55.540 --> 00:12:57.188 So the way this works is we absorb

00:12:57.188 --> 00:12:58.819 iron from the diet in the duodenum,

00:12:58.820 --> 00:13:01.200 about 1 to 2 milligrams per day.

00:13:01.200 --> 00:13:03.580 Iron circulates in the bloodstream,

00:13:03.580 --> 00:13:05.420 bound to a carrier protein

00:13:05.420 --> 00:13:06.156 called transferrin.

00:13:06.160 --> 00:13:08.472 This helps to keep iron inert and also

00:13:08.472 --> 00:13:11.183 helps it be delivered to all cells in the

00:13:11.183 --> 00:13:13.740 body via uptake via transparent receptors.

00:13:13.740 --> 00:13:15.890 But much of the iron does go into the bone

00:13:15.949 --> 00:13:18.253 marrow for the production of red blood cells.

00:13:18.260 --> 00:13:19.954 When the red blood cells get old,

00:13:19.960 --> 00:13:21.878 they get taken up into the macrophages,

00:13:21.880 --> 00:13:23.903 which can then recycle that iron and

NOTE Confidence: 0.844118134285714

00:13:23.903 --> 00:13:25.769 release it back into circulation.

NOTE Confidence: 0.844118134285714

00:13:25.770 --> 00:13:26.566 That's needed,

NOTE Confidence: 0.844118134285714

00:13:26.566 --> 00:13:28.954 we also get have iron storage

NOTE Confidence: 0.844118134285714

00:13:28.954 --> 00:13:31.710 in the liver and other tissues.

NOTE Confidence: 0.844118134285714

00:13:31.710 --> 00:13:33.900 Now it turns out that most of the iron is

NOTE Confidence: 0.844118134285714

00:13:33.953 --> 00:13:36.088 provided through this recycling process,

NOTE Confidence: 0.844118134285714

00:13:36.090 --> 00:13:38.645 about 20 to 25 milligrams per day,

NOTE Confidence: 0.844118134285714

00:13:38.650 --> 00:13:41.158 so really much more than what's

NOTE Confidence: 0.844118134285714

00:13:41.158 --> 00:13:42.830 provided through dietary absorption.

NOTE Confidence: 0.844118134285714

00:13:42.830 --> 00:13:44.510 And in fact the circulating pool

NOTE Confidence: 0.844118134285714

00:13:44.510 --> 00:13:46.330 of iron is actually quite small.

NOTE Confidence: 0.844118134285714

00:13:46.330 --> 00:13:47.710 It's only about 3 milligrams,

NOTE Confidence: 0.844118134285714

00:13:47.710 --> 00:13:48.570 so as you can see,

NOTE Confidence: 0.844118134285714

00:13:48.570 --> 00:13:50.481 you actually have to turn over the

NOTE Confidence: 0.844118134285714

00:13:50.481 --> 00:13:51.970 circulating pool about seven or eight

NOTE Confidence: 0.844118134285714

00:13:51.970 --> 00:13:54.093 times a day in order to meet the daily

NOTE Confidence: 0.844118134285714

00:13:54.093 --> 00:13:55.668 requirement for red cell production.

NOTE Confidence: 0.844118134285714

00:13:55.670 --> 00:13:56.392 And finally,

NOTE Confidence: 0.844118134285714

00:13:56.392 --> 00:13:58.197 there's really no regulated mechanism

NOTE Confidence: 0.844118134285714

00:13:58.197 --> 00:14:00.088 for iron removal from the body.

NOTE Confidence: 0.844118134285714

00:14:00.090 --> 00:14:01.730 We lose iron through bleeding

NOTE Confidence: 0.844118134285714

00:14:01.730 --> 00:14:03.042 through sloughing of cells,

NOTE Confidence: 0.844118134285714

00:14:03.050 --> 00:14:03.930 but for the most part,

NOTE Confidence: 0.844118134285714

00:14:03.930 --> 00:14:06.015 the regulation of iron homeostasis

NOTE Confidence: 0.844118134285714

00:14:06.015 --> 00:14:08.100 occurs through the regulation of

NOTE Confidence: 0.844118134285714

00:14:08.167 --> 00:14:10.183 the absorption from the diet and

NOTE Confidence: 0.844118134285714

00:14:10.183 --> 00:14:12.030 the release from body stores.

NOTE Confidence: 0.844118134285714

00:14:12.030 --> 00:14:13.878 And a key mediator of this process

NOTE Confidence: 0.844118134285714

00:14:13.878 --> 00:14:15.848 is a hormone called have decided,

NOTE Confidence: 0.844118134285714

00:14:15.850 --> 00:14:17.243 and we're going to talk a little

NOTE Confidence: 0.844118134285714

00:14:17.243 --> 00:14:18.608 bit more about this in a minute,

NOTE Confidence: 0.844118134285714

00:14:18.610 --> 00:14:20.346 but I just want to bring this

NOTE Confidence: 0.844118134285714

00:14:20.346 --> 00:14:22.110 back to kidney disease patients,

NOTE Confidence: 0.844118134285714

00:14:22.110 --> 00:14:24.150 so it turns out in kidney disease patients,

NOTE Confidence: 0.844118134285714

00:14:24.150 --> 00:14:26.114 there are numerous disturbances.

NOTE Confidence: 0.844118134285714

00:14:26.114 --> 00:14:28.078 And these homeostatic mechanisms,

NOTE Confidence: 0.844118134285714

00:14:28.080 --> 00:14:28.860 first of all,

NOTE Confidence: 0.844118134285714

00:14:28.860 --> 00:14:31.160 patients tend to be a negative iron balance.

NOTE Confidence: 0.844118134285714

00:14:31.160 --> 00:14:32.420 Particularly hemodialysis patients

NOTE Confidence: 0.844118134285714

00:14:32.420 --> 00:14:34.940 have been estimated to lose between

NOTE Confidence: 0.844118134285714

00:14:34.940 --> 00:14:37.353 one and a half to 3 grams of iron per

NOTE Confidence: 0.844118134285714

00:14:37.353 --> 00:14:39.618 year due to increased bleeding tendency.

NOTE Confidence: 0.844118134285714

00:14:39.620 --> 00:14:41.780 Blood trapping in the dialyzer tubing,

NOTE Confidence: 0.844118134285714

00:14:41.780 --> 00:14:45.740 frequent phlebotomy and many of our

NOTE Confidence: 0.844118134285714

00:14:45.740 --> 00:14:48.680 patients don't absorb don't get very much.

NOTE Confidence: 0.844118134285714

00:14:48.680 --> 00:14:49.472 A dietary iron.

NOTE Confidence: 0.844118134285714

00:14:49.472 --> 00:14:51.895 Some of this may be due to nutritional

NOTE Confidence: 0.844118134285714

00:14:51.895 --> 00:14:53.911 deficits or medications that

NOTE Confidence: 0.844118134285714

00:14:53.911 --> 00:14:55.927 interfere with iron absorption.

NOTE Confidence: 0.844118134285714

00:14:55.930 --> 00:14:57.470 But patients with kidney disease

NOTE Confidence: 0.844118134285714

00:14:57.470 --> 00:14:59.462 also have access levels of this

NOTE Confidence: 0.844118134285714

00:14:59.462 --> 00:15:01.050 iron regulatory hormone hepcidin,

NOTE Confidence: 0.844118134285714

00:15:01.050 --> 00:15:03.070 which actually also interferes

NOTE Confidence: 0.844118134285714

00:15:03.070 --> 00:15:04.585 with iron absorption.

NOTE Confidence: 0.844118134285714

00:15:04.590 --> 00:15:06.732 Now these problems can lead to

NOTE Confidence: 0.844118134285714

00:15:06.732 --> 00:15:08.790 a total body deficit of iron,

NOTE Confidence: 0.844118134285714

00:15:08.790 --> 00:15:10.430 something that we call absolute

NOTE Confidence: 0.844118134285714

00:15:10.430 --> 00:15:11.086 iron deficiency.

NOTE Confidence: 0.844118134285714

00:15:11.090 --> 00:15:13.474 And of course it makes sense to treat

NOTE Confidence: 0.844118134285714

00:15:13.474 --> 00:15:15.999 this by giving iron supplementation.

NOTE Confidence: 0.844118134285714

00:15:16.000 --> 00:15:18.156 But it turns out that the excess

NOTE Confidence: 0.844118134285714

00:15:18.156 --> 00:15:19.517 helpside levels also contribute

NOTE Confidence: 0.844118134285714

00:15:19.517 --> 00:15:21.779 to this problem of of reticulate

NOTE Confidence: 0.844118134285714

00:15:21.779 --> 00:15:23.500 endothelial cell iron blockade,

NOTE Confidence: 0.844118134285714

00:15:23.500 --> 00:15:25.474 whereby even though the stores of iron

NOTE Confidence: 0.844118134285714

00:15:25.474 --> 00:15:28.020 in the body may be adequate or even high,

NOTE Confidence: 0.844118134285714

00:15:28.020 --> 00:15:29.676 they stores are just not able

NOTE Confidence: 0.844118134285714

00:15:29.676 --> 00:15:31.520 to be released into circulation,

NOTE Confidence: 0.844118134285714

00:15:31.520 --> 00:15:32.680 at least not efficiently

NOTE Confidence: 0.844118134285714

00:15:32.680 --> 00:15:34.420 enough to meet the needs for

NOTE Confidence: 0.893422445384615

00:15:34.483 --> 00:15:35.578 red cell production.

NOTE Confidence: 0.893422445384615

00:15:35.580 --> 00:15:37.545 And this can be exacerbated

NOTE Confidence: 0.893422445384615

00:15:37.545 --> 00:15:39.478 when patients are on ASA's,

NOTE Confidence: 0.893422445384615

00:15:39.478 --> 00:15:41.626 which cause a rapid burst of

NOTE Confidence: 0.893422445384615

00:15:41.626 --> 00:15:42.700 erythropoiesis that rapidly

NOTE Confidence: 0.893422445384615

00:15:42.763 --> 00:15:44.195 deplete the circulating pool

NOTE Confidence: 0.893422445384615

00:15:44.195 --> 00:15:46.343 faster than it can be replenished.

NOTE Confidence: 0.893422445384615

00:15:46.350 --> 00:15:48.275 And this is a problem that we

NOTE Confidence: 0.893422445384615

00:15:48.275 --> 00:15:49.770 call functional iron deficiency,

NOTE Confidence: 0.893422445384615

00:15:49.770 --> 00:15:51.220 where it really the circulating

NOTE Confidence: 0.893422445384615

00:15:51.220 --> 00:15:53.253 pool of iron is limiting for with

NOTE Confidence: 0.893422445384615

00:15:53.253 --> 00:15:55.101 voices and for this entity it's less

NOTE Confidence: 0.893422445384615

00:15:55.101 --> 00:15:56.972 clear that iron supplementation is

NOTE Confidence: 0.893422445384615

00:15:56.972 --> 00:15:58.524 the right therapeutic strategy,

NOTE Confidence: 0.893422445384615

00:15:58.530 --> 00:16:00.308 as we we might worry that giving

NOTE Confidence: 0.893422445384615

00:16:00.308 --> 00:16:01.966 patients more and more iron may

NOTE Confidence: 0.893422445384615

00:16:01.966 --> 00:16:03.658 lead to problems with iron overload,

NOTE Confidence: 0.893422445384615

00:16:03.660 --> 00:16:05.172 and so for this reason I think

NOTE Confidence: 0.893422445384615

00:16:05.172 --> 00:16:06.468 it's helpful to understand a

NOTE Confidence: 0.893422445384615

00:16:06.468 --> 00:16:07.948 little bit more about hepcidin,

NOTE Confidence: 0.893422445384615

00:16:07.950 --> 00:16:09.505 biology and and thinking about

NOTE Confidence: 0.893422445384615

00:16:09.505 --> 00:16:11.990 whether this may be a different way

NOTE Confidence: 0.893422445384615

00:16:11.990 --> 00:16:14.165 of of targeting this therapeutically.

NOTE Confidence: 0.893422445384615

00:16:14.170 --> 00:16:15.462 So what is subsiding?

NOTE Confidence: 0.893422445384615

00:16:15.462 --> 00:16:17.077 It's a 25 amino acid.

NOTE Confidence: 0.893422445384615

00:16:17.080 --> 00:16:18.720 Peptide hormone that's made by

NOTE Confidence: 0.893422445384615

00:16:18.720 --> 00:16:20.716 the liver circulates in the blood

NOTE Confidence: 0.893422445384615

00:16:20.716 --> 00:16:22.510 and is excreted by the kidneys.

NOTE Confidence: 0.893422445384615

00:16:22.510 --> 00:16:24.175 The function of hepcidin is

NOTE Confidence: 0.893422445384615

00:16:24.175 --> 00:16:25.507 illustrated in this slide,

NOTE Confidence: 0.893422445384615

00:16:25.510 --> 00:16:27.498 So what I'm showing you here is

NOTE Confidence: 0.893422445384615

00:16:27.498 --> 00:16:28.996 the enterocyte that absorbs iron

NOTE Confidence: 0.893422445384615

00:16:28.996 --> 00:16:30.466 in the in the intestine,

NOTE Confidence: 0.893422445384615

00:16:30.470 --> 00:16:32.558 so elemental iron is taken up

NOTE Confidence: 0.893422445384615

00:16:32.558 --> 00:16:34.414 across the apical surface through

NOTE Confidence: 0.893422445384615

00:16:34.414 --> 00:16:36.369 a transporter called DMT one.

NOTE Confidence: 0.893422445384615

00:16:36.370 --> 00:16:37.398 Once inside the cell,

NOTE Confidence: 0.893422445384615

00:16:37.398 --> 00:16:39.345 iron can be used by that cell

NOTE Confidence: 0.893422445384615

00:16:39.345 --> 00:16:41.070 for its old metabolic processes,

NOTE Confidence: 0.893422445384615

00:16:41.070 --> 00:16:42.070 or if it's not needed,

NOTE Confidence: 0.893422445384615

00:16:42.070 --> 00:16:44.506 it'll get stored in early in ferritin,

NOTE Confidence: 0.893422445384615

00:16:44.510 --> 00:16:46.094 which is the iron storage protein

NOTE Confidence: 0.893422445384615

00:16:46.094 --> 00:16:47.680 and all cells in our body.

NOTE Confidence: 0.893422445384615

00:16:47.680 --> 00:16:48.576 And if this happens,

NOTE Confidence: 0.893422445384615

00:16:48.576 --> 00:16:50.474 this iron is going to get lost as

NOTE Confidence: 0.893422445384615

00:16:50.474 --> 00:16:52.498 these cells get sloughed off every few days.

NOTE Confidence: 0.893422445384615

00:16:52.500 --> 00:16:54.229 In order for that iron to be

NOTE Confidence: 0.893422445384615

00:16:54.229 --> 00:16:56.000 accessible to the Organism at large,

NOTE Confidence: 0.893422445384615

00:16:56.000 --> 00:16:58.590 it needs to be exported across the

NOTE Confidence: 0.893422445384615

00:16:58.590 --> 00:17:00.604 basolateral surface through an iron

NOTE Confidence: 0.893422445384615

00:17:00.604 --> 00:17:02.276 export protein called ferroportin.

NOTE Confidence: 0.893422445384615

00:17:02.280 --> 00:17:02.932 The macrophages,

NOTE Confidence: 0.893422445384615

00:17:02.932 --> 00:17:04.888 which recycle iron from the red

NOTE Confidence: 0.893422445384615

00:17:04.888 --> 00:17:07.062 cells again for that iron to be

NOTE Confidence: 0.893422445384615

00:17:07.062 --> 00:17:08.527 released back into the circulation

NOTE Confidence: 0.893422445384615

00:17:08.588 --> 00:17:10.310 and also needs to go through

NOTE Confidence: 0.893422445384615

00:17:10.310 --> 00:17:12.620 Fairport so Fairport has really the

NOTE Confidence: 0.893422445384615

00:17:12.620 --> 00:17:14.640 gatekeeper that controls iron entry

NOTE Confidence: 0.893422445384615

00:17:14.710 --> 00:17:16.744 into the circulation both from the

NOTE Confidence: 0.893422445384615

00:17:16.744 --> 00:17:18.949 diet and from the body stores.

NOTE Confidence: 0.893422445384615

00:17:18.950 --> 00:17:20.606 So the function of hepcidin is

NOTE Confidence: 0.893422445384615

00:17:20.606 --> 00:17:22.400 illustrated by this nice cryoem image

NOTE Confidence: 0.893422445384615

00:17:22.400 --> 00:17:24.320 that was published recently in nature,

NOTE Confidence: 0.893422445384615

00:17:24.320 --> 00:17:26.140 where and you can see here have

NOTE Confidence: 0.893422445384615

00:17:26.140 --> 00:17:27.535 siding this colored in orange

NOTE Confidence: 0.893422445384615

00:17:27.535 --> 00:17:28.655 and Fairport and green,

NOTE Confidence: 0.893422445384615

00:17:28.660 --> 00:17:31.068 and what you can see is that hepcidin

NOTE Confidence: 0.893422445384615

00:17:31.068 --> 00:17:32.693 actually binds directly to the

NOTE Confidence: 0.893422445384615

00:17:32.693 --> 00:17:34.607 central cavity of Fairport and where

NOTE Confidence: 0.893422445384615

33

00:17:34.607 --> 00:17:36.609 it blocks iron export directly.

NOTE Confidence: 0.893422445384615

00:17:36.610 --> 00:17:38.962 Peptide binding to Fairport and also

NOTE Confidence: 0.893422445384615

00:17:38.962 --> 00:17:40.530 induces the internalization and

NOTE Confidence: 0.893422445384615

00:17:40.591 --> 00:17:42.831 degradation of Fairport and thereby

NOTE Confidence: 0.893422445384615

00:17:42.831 --> 00:17:44.623 furthering inhibiting iron export.

NOTE Confidence: 0.893422445384615

00:17:44.630 --> 00:17:46.660 So the consequence of this is that

NOTE Confidence: 0.893422445384615

00:17:46.660 --> 00:17:48.237 when hepcidin levels are high

NOTE Confidence: 0.893422445384615

00:17:48.237 --> 00:17:49.537 it binds ferroportin blocks.

NOTE Confidence: 0.893422445384615

00:17:49.540 --> 00:17:51.856 Iron export induces the degradation of

NOTE Confidence: 0.893422445384615

00:17:51.856 --> 00:17:54.720 Fairport and to further inhibit iron export,

NOTE Confidence: 0.893422445384615

00:17:54.720 --> 00:17:56.208 thereby leading to reduced

NOTE Confidence: 0.893422445384615

00:17:56.208 --> 00:17:57.696 circulating levels of iron.

NOTE Confidence: 0.893422445384615

00:17:57.700 --> 00:17:59.045 And when this happens chronically

NOTE Confidence: 0.893422445384615

00:17:59.045 --> 00:18:00.716 this can lead to iron restricted

NOTE Confidence: 0.893422445384615

00:18:00.716 --> 00:18:02.868 with voices and anemia as we see for

NOTE Confidence: 0.893422445384615

00:18:02.868 --> 00:18:04.310 example in kidney disease patients

NOTE Confidence: 0.893422445384615

00:18:04.310 --> 00:18:07.142 even though the stores of iron in the body.

NOTE Confidence: 0.893422445384615

00:18:07.142 --> 00:18:08.678 Maybe normal or high?

NOTE Confidence: 0.893422445384615

00:18:08.680 --> 00:18:10.665 Low hepcidin actually leads to

NOTE Confidence: 0.893422445384615

00:18:10.665 --> 00:18:11.856 the opposite situation.

NOTE Confidence: 0.893422445384615

00:18:11.860 --> 00:18:13.304 There's unregulated Fairport and

NOTE Confidence: 0.893422445384615

00:18:13.304 --> 00:18:15.470 expression you can't turn off the

NOTE Confidence: 0.893422445384615

00:18:15.532 --> 00:18:17.338 absorption of iron from the diet.

NOTE Confidence: 0.858139689166667

00:18:17.340 --> 00:18:19.104 Iron is continually released from the

NOTE Confidence: 0.858139689166667

00:18:19.104 --> 00:18:20.819 cells designed to store it safely.

NOTE Confidence: 0.858139689166667

00:18:20.820 --> 00:18:22.822 The macrophages and this excess iron then

NOTE Confidence: 0.858139689166667

00:18:22.822 --> 00:18:24.785 can deposit in other tissues where it

NOTE Confidence: 0.858139689166667

00:18:24.785 --> 00:18:27.020 can lead to organ damage and dysfunction,

NOTE Confidence: 0.858139689166667

00:18:27.020 --> 00:18:29.024 and this is really the underlying

NOTE Confidence: 0.858139689166667

00:18:29.024 --> 00:18:30.360 pathophysiology of of iron

NOTE Confidence: 0.858139689166667

00:18:30.416 --> 00:18:32.030 overload and hemochromatosis,

NOTE Confidence: 0.858139689166667

00:18:32.030 --> 00:18:35.838 as well as thalassemia.

NOTE Confidence: 0.858139689166667

00:18:35.840 --> 00:18:37.688 Now as a key regulator of

NOTE Confidence: 0.858139689166667

00:18:37.688 --> 00:18:38.612 systemic iron homeostasis,

NOTE Confidence: 0.858139689166667

00:18:38.620 --> 00:18:40.587 the production of peptide and the liver

NOTE Confidence: 0.858139689166667

00:18:40.587 --> 00:18:42.720 is regulated by a number of key signals.

NOTE Confidence: 0.858139689166667

00:18:42.720 --> 00:18:43.544 So one is iron.

NOTE Confidence: 0.858139689166667

00:18:43.544 --> 00:18:45.490 So if you give a patient and I an

NOTE Confidence: 0.858139689166667

00:18:45.490 --> 00:18:47.320 injection of iron or take an iron pill,

NOTE Confidence: 0.858139689166667

00:18:47.320 --> 00:18:49.200 this will induce Obsidian to

NOTE Confidence: 0.858139689166667

00:18:49.200 --> 00:18:51.080 inhibit fair portion to inhibit

NOTE Confidence: 0.858139689166667

00:18:51.144 --> 00:18:52.900 iron absorption and release.

NOTE Confidence: 0.858139689166667

00:18:52.900 --> 00:18:55.294 This helps to maintain the steady state.

NOTE Confidence: 0.858139689166667

00:18:55.300 --> 00:18:56.952 Iron deficiency suppresses have

NOTE Confidence: 0.858139689166667

00:18:56.952 --> 00:18:59.017 decided to increase iron availability,

NOTE Confidence: 0.858139689166667

00:18:59.020 --> 00:19:01.576 again, keeping you in steady state.

NOTE Confidence: 0.858139689166667

00:19:01.580 --> 00:19:03.280 Anything that increases the risk

NOTE Confidence: 0.858139689166667

00:19:03.280 --> 00:19:05.300 aquatic drive. So this would be anemia.

NOTE Confidence: 0.858139689166667

00:19:05.300 --> 00:19:06.977 Hypoxia, erythropoietin injections.

NOTE Confidence: 0.858139689166667

00:19:06.977 --> 00:19:10.331 These all suppress upside and thereby

NOTE Confidence: 0.858139689166667

00:19:10.331 --> 00:19:12.286 increasing iron availability to

NOTE Confidence: 0.858139689166667

00:19:12.286 --> 00:19:14.944 support the needed red cell production.

NOTE Confidence: 0.858139689166667

00:19:14.950 --> 00:19:15.754 And finally,

NOTE Confidence: 0.858139689166667

00:19:15.754 --> 00:19:17.362 inflammation is a stimulator

NOTE Confidence: 0.858139689166667

00:19:17.362 --> 00:19:18.568 of hepcidin production.

NOTE Confidence: 0.858139689166667

00:19:18.570 --> 00:19:20.098 This likely developed evolutionarily

NOTE Confidence: 0.858139689166667

00:19:20.098 --> 00:19:22.390 as a protective mechanism to sequester

NOTE Confidence: 0.858139689166667

00:19:22.444 --> 00:19:23.844 iron from invading pathogens that

NOTE Confidence: 0.858139689166667

00:19:23.844 --> 00:19:25.910 need iron to grow and proliferate.

NOTE Confidence: 0.858139689166667

00:19:25.910 --> 00:19:27.390 But it's this pathway that,

NOTE Confidence: 0.858139689166667

00:19:27.390 --> 00:19:28.960 in the setting of chronic

NOTE Confidence: 0.858139689166667

00:19:28.960 --> 00:19:29.588 inflammatory diseases,

NOTE Confidence: 0.858139689166667

00:19:29.590 --> 00:19:31.680 can contribute to iron restricted

NOTE Confidence: 0.858139689166667

00:19:31.680 --> 00:19:33.352 with prices and anemia.

NOTE Confidence: 0.858139689166667

00:19:33.360 --> 00:19:34.064 And indeed,

NOTE Confidence: 0.858139689166667

00:19:34.064 --> 00:19:35.472 kidney disease patients do

NOTE Confidence: 0.858139689166667

00:19:35.472 --> 00:19:36.880 have excess upside levels.

NOTE Confidence: 0.858139689166667

00:19:36.880 --> 00:19:37.693 That's been illustrated

NOTE Confidence: 0.858139689166667

00:19:37.693 --> 00:19:39.048 by a number of studies.

NOTE Confidence: 0.858139689166667

00:19:39.050 --> 00:19:40.778 This is one such study in Ashby at all,

NOTE Confidence: 0.858139689166667

00:19:40.780 --> 00:19:42.468 showing that hemodialysis patients

NOTE Confidence: 0.858139689166667

00:19:42.468 --> 00:19:45.000 have much higher levels of circulating

NOTE Confidence: 0.858139689166667

00:19:45.064 --> 00:19:46.914 hepcidin compared to control patients

NOTE Confidence: 0.858139689166667

00:19:46.914 --> 00:19:49.579 and then patients with non dialysis CKD.

NOTE Confidence: 0.858139689166667

00:19:49.580 --> 00:19:51.520 There's an inverse correlation between

NOTE Confidence: 0.858139689166667

00:19:51.520 --> 00:19:53.460 estimated GFR and upside down,

NOTE Confidence: 0.858139689166667

00:19:53.460 --> 00:19:54.528 and again there's probably

NOTE Confidence: 0.858139689166667

00:19:54.528 --> 00:19:55.596 2 mechanisms for this.

NOTE Confidence: 0.858139689166667

00:19:55.600 --> 00:19:57.460 Hepcidin is up regulated by inflammation,

NOTE Confidence: 0.858139689166667

00:19:57.460 --> 00:19:59.566 so the inflammatory milieu of CKD

NOTE Confidence: 0.858139689166667

00:19:59.566 --> 00:20:00.970 and hemodialysis can stimulate

NOTE Confidence: 0.858139689166667

00:20:01.028 --> 00:20:02.671 herbicide and production, and,

NOTE Confidence: 0.858139689166667

00:20:02.671 --> 00:20:04.297 you know, as a small peptoid.

NOTE Confidence: 0.858139689166667

00:20:04.300 --> 00:20:05.950 Form an excreted by the kidneys,

NOTE Confidence: 0.858139689166667

00:20:05.950 --> 00:20:07.380 kidney disease can lead to

NOTE Confidence: 0.858139689166667

00:20:07.380 --> 00:20:08.524 reduced herbicide and clearance,

NOTE Confidence: 0.858139689166667

00:20:08.530 --> 00:20:10.770 which can also contribute to excess levels.

NOTE Confidence: 0.850496976

00:20:12.970 --> 00:20:14.790 So what our group has been interested

NOTE Confidence: 0.850496976

00:20:14.790 --> 00:20:16.997 in is trying to understand how is it

NOTE Confidence: 0.850496976

00:20:16.997 --> 00:20:19.210 that the liver integrates all of these

NOTE Confidence: 0.850496976

00:20:19.210 --> 00:20:20.770 different signals to appropriately

NOTE Confidence: 0.850496976

00:20:20.770 --> 00:20:22.330 regulate upside and production.

NOTE Confidence: 0.850496976

00:20:22.330 --> 00:20:23.401 And that's what I'm going to talk

NOTE Confidence: 0.850496976

00:20:23.401 --> 00:20:24.740 to you a little bit about today,

NOTE Confidence: 0.850496976

00:20:24.740 --> 00:20:26.972 and then can we think about

NOTE Confidence: 0.850496976

00:20:26.972 --> 00:20:28.088 using this therapeutically?

NOTE Confidence: 0.850496976

00:20:28.090 --> 00:20:28.924 Potentially so?

NOTE Confidence: 0.850496976

00:20:28.924 --> 00:20:31.843 First, let's talk about the iron signal,

NOTE Confidence: 0.850496976

00:20:31.850 --> 00:20:33.605 so clues for understanding how

NOTE Confidence: 0.850496976

00:20:33.605 --> 00:20:35.009 iron regulate hepcidin come

NOTE Confidence: 0.850496976

00:20:35.009 --> 00:20:36.929 from hereditary hemochromatosis.

NOTE Confidence: 0.850496976

00:20:36.930 --> 00:20:38.910 We mean we discuss this briefly.

NOTE Confidence: 0.850496976

00:20:38.910 --> 00:20:41.126 This has caused a disorder of iron overload

NOTE Confidence: 0.850496976

00:20:41.126 --> 00:20:43.515 caused by mutations in one of several genes.

NOTE Confidence: 0.850496976

00:20:43.520 --> 00:20:46.859 So mutation in HFE are the most common cause.

NOTE Confidence: 0.850496976

00:20:46.860 --> 00:20:48.780 Transparent receptor 2 causes of more

NOTE Confidence: 0.850496976

00:20:48.780 --> 00:20:50.961 rare adult onset form of this disease

NOTE Confidence: 0.850496976

00:20:50.961 --> 00:20:52.935 and mutations and have side in Excel

NOTE Confidence: 0.850496976

00:20:52.990 --> 00:20:55.041 or another gene called him a jubilant

NOTE Confidence: 0.850496976

00:20:55.041 --> 00:20:57.460 actually cause a more rare but more

NOTE Confidence: 0.850496976

00:20:57.460 --> 00:21:00.430 severe juvenile onset form of this disease.

NOTE Confidence: 0.850496976

00:21:00.430 --> 00:21:02.355 All patients who have mutations in any

NOTE Confidence: 0.850496976

00:21:02.355 --> 00:21:04.508 of these genes have the same problem and

NOTE Confidence: 0.850496976

00:21:04.508 --> 00:21:06.484 this is a deficiency of hepcidin that

NOTE Confidence: 0.850496976

00:21:06.484 --> 00:21:08.745 fails to be appropriately induced by iron,

NOTE Confidence: 0.850496976

00:21:08.750 --> 00:21:10.418 so that's illustrated in this slide

NOTE Confidence: 0.850496976

00:21:10.418 --> 00:21:12.869 so you can see that these these these,

NOTE Confidence: 0.850496976

00:21:12.870 --> 00:21:14.241 these proteins HIV

NOTE Confidence: 0.850496976

00:21:14.241 --> 00:21:16.069 transferred to human javelin.

NOTE Confidence: 0.850496976

00:21:16.070 --> 00:21:17.948 They're all expressed in the liver,

NOTE Confidence: 0.850496976

00:21:17.950 --> 00:21:20.486 and so somehow they must be involved in

NOTE Confidence: 0.850496976

00:21:20.486 --> 00:21:22.915 sensing iron levels and transducing that

NOTE Confidence: 0.850496976

00:21:22.915 --> 00:21:25.513 signal to appropriately regulate upside and

NOTE Confidence: 0.850496976

00:21:25.575 --> 00:21:28.315 and so that if any of these genes is mutated,

NOTE Confidence: 0.850496976

00:21:28.320 --> 00:21:29.940 this leads to hepcidin

NOTE Confidence: 0.850496976

00:21:29.940 --> 00:21:31.560 deficiency in iron overload.

NOTE Confidence: 0.850496976

00:21:31.560 --> 00:21:33.639 Now we got into this field because we were

NOTE Confidence: 0.850496976

00:21:33.639 --> 00:21:35.556 studying him adjuvant for a different reason,

NOTE Confidence: 0.850496976

00:21:35.560 --> 00:21:37.583 and that's because it's a family member

NOTE Confidence: 0.850496976

00:21:37.583 --> 00:21:40.220 of a family of three genes called the

NOTE Confidence: 0.850496976

00:21:40.220 --> 00:21:42.380 repulsive guidance molecule or RGM family,

NOTE Confidence: 0.850496976

00:21:42.380 --> 00:21:44.666 which in work that I did as a postdoc

NOTE Confidence: 0.850496976

00:21:44.666 --> 00:21:47.159 in Hartland's lab we showed function as

NOTE Confidence: 0.850496976

00:21:47.159 --> 00:21:49.618 Co receptors for the bull morphogenetic

NOTE Confidence: 0.850496976

00:21:49.618 --> 00:21:51.978 protein or BMP signaling pathway.

NOTE Confidence: 0.850496976

00:21:51.980 --> 00:21:53.350 So what are BMPS there?

NOTE Confidence: 0.850496976

00:21:53.350 --> 00:21:55.198 There are some family of the Tiger

NOTE Confidence: 0.850496976

00:21:55.198 --> 00:21:56.440 beta superfamily of ligands,

NOTE Confidence: 0.850496976

00:21:56.440 --> 00:21:59.527 which is a super family of over 40 members

NOTE Confidence: 0.850496976

00:21:59.527 --> 00:22:01.987 including TGF Betas and BMP's themselves.

NOTE Confidence: 0.850496976

00:22:01.990 --> 00:22:03.875 As well as malaria and

NOTE Confidence: 0.850496976

00:22:03.875 --> 00:22:05.006 inhibiting substance activists,

NOTE Confidence: 0.850496976

00:22:05.010 --> 00:22:07.130 inhibitions and growth in

NOTE Confidence: 0.850496976

00:22:07.130 --> 00:22:08.190 differentiation factors,

NOTE Confidence: 0.850496976

00:22:08.190 --> 00:22:10.773 these are disulfide and dimers that share

NOTE Confidence: 0.850496976

00:22:10.773 --> 00:22:12.584 overall structural similarities and a

NOTE Confidence: 0.850496976

00:22:12.584 --> 00:22:14.209 common paradigm of signal transduction.

NOTE Confidence: 0.850496976

00:22:14.210 --> 00:22:16.359 Where the login will bind to a

NOTE Confidence: 0.850496976

00:22:16.359 --> 00:22:18.741 complex of two type one and two

NOTE Confidence: 0.850496976

00:22:18.741 --> 00:22:20.829 Type 2 serine 39 kinase receptors.

NOTE Confidence: 0.850496976

00:22:20.830 --> 00:22:22.470 Upon formation of the complex,

NOTE Confidence: 0.850496976

00:22:22.470 --> 00:22:24.318 the Type 2 receptors flex sporulate,

NOTE Confidence: 0.850496976

00:22:24.320 --> 00:22:26.882 the Type 1 receptors which then

NOTE Confidence: 0.850496976

00:22:26.882 --> 00:22:28.590 phosphorylate interest sosmed proteins.

NOTE Confidence: 0.850496976

00:22:28.590 --> 00:22:30.590 There are two subsets of smeds Med 1/5

NOTE Confidence: 0.850496976

00:22:30.590 --> 00:22:32.770 and eight that are activated by the beam.

NOTE Confidence: 0.850496976

00:22:32.770 --> 00:22:33.998 Keys and some ads.

NOTE Confidence: 0.850496976

00:22:33.998 --> 00:22:35.840 Two and three that are activated

NOTE Confidence: 0.850496976

00:22:35.910 --> 00:22:37.540 by activists and TGF fades.

NOTE Confidence: 0.850496976

00:22:37.540 --> 00:22:39.310 These form a complex with the

NOTE Confidence: 0.850496976

00:22:39.310 --> 00:22:39.900 common mediators.

NOTE Confidence: 0.850496976

00:22:39.900 --> 00:22:42.054 Med four and these are transcription

NOTE Confidence: 0.850496976

00:22:42.054 --> 00:22:44.332 factors that that migrate to the

NOTE Confidence: 0.850496976

00:22:44.332 --> 00:22:46.277 nucleus and regulate gene transcription,

NOTE Confidence: 0.850496976

00:22:46.280 --> 00:22:48.908 leading to a diverse array of

NOTE Confidence: 0.850496976

00:22:48.908 --> 00:22:49.784 biological functions.

NOTE Confidence: 0.850496976

00:22:49.790 --> 00:22:50.770 Now, as I mentioned,

NOTE Confidence: 0.850496976

00:22:50.770 --> 00:22:52.535 there's over 40 ligands and one of

NOTE Confidence: 0.850496976

00:22:52.535 --> 00:22:53.760 the interesting questions in this

NOTE Confidence: 0.850496976

00:22:53.760 --> 00:22:55.658 field is how is it that these ligands

NOTE Confidence: 0.850496976

00:22:55.658 --> 00:22:56.960 are able to lead to this

NOTE Confidence: 0.90598948

00:22:56.960 --> 00:22:59.430 diverse array of biological functions

NOTE Confidence: 0.90598948

00:22:59.430 --> 00:23:02.989 with a very limited subset of receptors?

NOTE Confidence: 0.90598948

00:23:02.990 --> 00:23:05.720 So there's only five Type 2 receptors,

NOTE Confidence: 0.90598948

00:23:05.720 --> 00:23:07.524 7 type 1 receptors,

NOTE Confidence: 0.90598948

00:23:07.524 --> 00:23:11.150 and these two subsets of SMAD proteins.

NOTE Confidence: 0.90598948

00:23:11.150 --> 00:23:12.473 And at least part of the answer

NOTE Confidence: 0.90598948

00:23:12.473 --> 00:23:13.818 to that question is that there's

NOTE Confidence: 0.90598948

00:23:13.818 --> 00:23:14.790 regulation of this pathway.

NOTE Confidence: 0.90598948

00:23:14.790 --> 00:23:16.360 A number of different levels

NOTE Confidence: 0.90598948

00:23:16.360 --> 00:23:17.616 from the extracellular surface,

NOTE Confidence: 0.90598948

00:23:17.620 --> 00:23:19.588 which we'll hear a little bit about later,

NOTE Confidence: 0.90598948

00:23:19.590 --> 00:23:22.092 so the membrane surface to intracellularly

NOTE Confidence: 0.90598948

00:23:22.092 --> 00:23:25.184 and one of the the levels of

NOTE Confidence: 0.90598948

00:23:25.184 --> 00:23:27.424 regulation is through Co receptors.

NOTE Confidence: 0.90598948

00:23:27.430 --> 00:23:28.750 And this is where our data

NOTE Confidence: 0.90598948

00:23:28.750 --> 00:23:29.823 suggests that HEMA, jubilant,

NOTE Confidence: 0.90598948

00:23:29.823 --> 00:23:33.127 and the other GM's are functioning as Co

NOTE Confidence: 0.90598948

00:23:33.127 --> 00:23:35.819 receptors for the BMP side of the pathway.

NOTE Confidence: 0.90598948

00:23:35.820 --> 00:23:37.188 And this is based on data

NOTE Confidence: 0.90598948

00:23:37.188 --> 00:23:38.100 such as the following.

NOTE Confidence: 0.90598948

00:23:38.100 --> 00:23:40.284 So if we take liver cells and culture

NOTE Confidence: 0.90598948

00:23:40.284 --> 00:23:43.185 and we transfect them with the BMP

NOTE Confidence: 0.90598948

00:23:43.185 --> 00:23:44.559 responsive luciferase reporter,

NOTE Confidence: 0.90598948

00:23:44.560 --> 00:23:46.438 when we add in exogenous BMP

NOTE Confidence: 0.90598948

00:23:46.438 --> 00:23:48.568 ligands we get an increase in

NOTE Confidence: 0.90598948

00:23:48.568 --> 00:23:50.980 luciferase activity and we see a

NOTE Confidence: 0.90598948

00:23:50.980 --> 00:23:53.271 similar effect if if we transfect

NOTE Confidence: 0.90598948

00:23:53.271 --> 00:23:55.395 in C DNA encoding human juggling.

NOTE Confidence: 0.90598948

00:23:55.400 --> 00:23:57.206 This is specific for the BMP side

NOTE Confidence: 0.90598948

00:23:57.206 --> 00:23:59.226 of the pathway because if we use

NOTE Confidence: 0.90598948

00:23:59.226 --> 00:24:00.410 another reporter that responds

NOTE Confidence: 0.90598948

00:24:00.410 --> 00:24:02.410 to TGF beta signals for example,

NOTE Confidence: 0.90598948

00:24:02.410 --> 00:24:04.774 we don't see any effect from

NOTE Confidence: 0.90598948

00:24:04.774 --> 00:24:05.956 human junelyn transfection.

NOTE Confidence: 0.90598948

00:24:05.960 --> 00:24:08.158 And we showed that this is working

NOTE Confidence: 0.90598948

00:24:08.158 --> 00:24:10.100 through the canonical BMP SMAD signaling

NOTE Confidence: 0.90598948

00:24:10.100 --> 00:24:12.298 pathway that I showed to you through.

NOTE Confidence: 0.90598948

00:24:12.300 --> 00:24:14.800 Endogenously expressed the empty lagans,

NOTE Confidence: 0.90598948

00:24:14.800 --> 00:24:16.180 the empty receptors and BMP

NOTE Confidence: 0.90598948

00:24:16.180 --> 00:24:18.209 smads because if we knock down or

NOTE Confidence: 0.90598948

00:24:18.209 --> 00:24:19.694 inhibit any of these components,

NOTE Confidence: 0.90598948

00:24:19.700 --> 00:24:21.396 this blocks the signaling.

NOTE Confidence: 0.90598948

00:24:21.396 --> 00:24:24.410 Now as I was generating this data,

NOTE Confidence: 0.90598948

00:24:24.410 --> 00:24:26.618 a paper came out linking mutations

NOTE Confidence: 0.90598948

00:24:26.618 --> 00:24:29.260 and HEMA juvelen to hemochromatosis.

NOTE Confidence: 0.90598948

00:24:29.260 --> 00:24:31.066 So we asked ourselves the obvious question,

NOTE Confidence: 0.90598948

00:24:31.070 --> 00:24:33.730 is this BMP signaling function of human

NOTE Confidence: 0.90598948

00:24:33.730 --> 00:24:35.670 javelin somehow important for its

NOTE Confidence: 0.90598948

00:24:35.670 --> 00:24:37.510 role in iron homeostasis regulation?

NOTE Confidence: 0.90598948

00:24:37.510 --> 00:24:38.107 And of course,

NOTE Confidence: 0.90598948

00:24:38.107 --> 00:24:39.301 the role that we thought about

NOTE Confidence: 0.90598948

00:24:39.301 --> 00:24:40.767 was in the regulation of hepcidin.

NOTE Confidence: 0.90598948

00:24:40.770 --> 00:24:42.570 Since this is where human Julian

NOTE Confidence: 0.90598948

00:24:42.570 --> 00:24:43.770 was proposed to act,

NOTE Confidence: 0.90598948

00:24:43.770 --> 00:24:45.632 and indeed we found that the MP's

NOTE Confidence: 0.90598948

00:24:45.632 --> 00:24:47.418 are quite potent stimulators of

NOTE Confidence: 0.90598948

00:24:47.418 --> 00:24:48.350 hepcidin production.

NOTE Confidence: 0.90598948

00:24:48.350 --> 00:24:50.275 So this is another cell culture assay

NOTE Confidence: 0.90598948

00:24:50.275 --> 00:24:52.050 using liver cells and we treat them.

NOTE Confidence: 0.90598948

00:24:52.050 --> 00:24:54.160 What different Joe Biden super

NOTE Confidence: 0.90598948

00:24:54.160 --> 00:24:56.270 family ligands and measure hepcidin

NOTE Confidence: 0.90598948

00:24:56.335 --> 00:24:58.542 by Q PCR and you can see that BMP's

48

00:24:58.542 --> 00:25:01.006 induced have siding by 200 to 1000

00:25:01.006 --> 00:25:03.396 folds and many BMP's can do this,

00:25:03.400 --> 00:25:06.390 including BMP, 24567 and nine,

00:25:06.390 --> 00:25:08.561 but it's really the BMP is rather

00:25:08.561 --> 00:25:10.589 than the other Super family members

00:25:10.589 --> 00:25:12.944 of the most robust inducers of

00:25:12.944 --> 00:25:14.762 hepcidin and it was subsequently

00:25:14.762 --> 00:25:16.850 shown that this is acting directly

00:25:16.910 --> 00:25:18.590 to transcriptional level through

00:25:18.590 --> 00:25:20.690 two specific SMAD binding elements

00:25:20.690 --> 00:25:22.490 in the hepcidin promoter.

00:25:22.490 --> 00:25:24.992 Now subsequently we were interested in

00:25:24.992 --> 00:25:27.167 understanding which of these ligands

00:25:27.167 --> 00:25:29.347 is important endogenously in vivo,

00:25:29.350 --> 00:25:29.653 right?

00:25:29.653 --> 00:25:31.168 If we add them exogenously,

NOTE Confidence: 0.90598948

00:25:31.170 --> 00:25:32.568 many of them can induce subsided,

NOTE Confidence: 0.90598948

00:25:32.570 --> 00:25:34.526 but which ones are really the

NOTE Confidence: 0.90598948

00:25:34.526 --> 00:25:35.830 important players in vivo?

NOTE Confidence: 0.90598948

00:25:35.830 --> 00:25:38.270 So clues for this came from 2 avenues.

NOTE Confidence: 0.90598948

00:25:38.270 --> 00:25:38.790 One was,

NOTE Confidence: 0.90598948

00:25:38.790 --> 00:25:40.610 some was from our work looking at

NOTE Confidence: 0.90598948

00:25:40.610 --> 00:25:42.690 the binding affinity of the different

NOTE Confidence: 0.90598948

00:25:42.690 --> 00:25:44.445 RGM proteins to BMP ligands.

NOTE Confidence: 0.90598948

00:25:44.450 --> 00:25:45.746 In our initial paper,

NOTE Confidence: 0.90598948

00:25:45.746 --> 00:25:47.690 we had demonstrated that our GM

NOTE Confidence: 0.90598948

00:25:47.756 --> 00:25:49.346 proteins bind directly to the

NOTE Confidence: 0.90598948

00:25:49.346 --> 00:25:50.936 ligands and and and in

NOTE Confidence: 0.68272287375

00:25:50.940 --> 00:25:52.134 2015 Christian Siebold.

NOTE Confidence: 0.68272287375

00:25:52.134 --> 00:25:53.726 They're actually published a

NOTE Confidence: 0.68272287375

00:25:53.726 --> 00:25:55.318 beautiful crystal structure showing

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NOTE Confidence: 0.68272287375

00:25:55.318 --> 00:25:57.058 this that the binding interaction.

NOTE Confidence: 0.68272287375

00:25:57.060 --> 00:25:58.885 This is our data using

NOTE Confidence: 0.68272287375

00:25:58.885 --> 00:25:59.980 surface plasmon resonance.

NOTE Confidence: 0.68272287375

00:25:59.980 --> 00:26:01.996 What we did is we compared the binding

NOTE Confidence: 0.68272287375

00:26:01.996 --> 00:26:03.741 affinity of the different RGM for

NOTE Confidence: 0.68272287375

00:26:03.741 --> 00:26:05.523 the different BMP ligands and they're

NOTE Confidence: 0.68272287375

00:26:05.579 --> 00:26:07.319 colored differently based on their

NOTE Confidence: 0.68272287375

00:26:07.319 --> 00:26:09.059 different subfamilies and what you

NOTE Confidence: 0.68272287375

00:26:09.060 --> 00:26:11.924 can see is that all of the RGM's had

NOTE Confidence: 0.68272287375

00:26:11.924 --> 00:26:13.976 the relatively highest affinity for BMP,

NOTE Confidence: 0.68272287375

00:26:13.980 --> 00:26:14.766 two and four,

NOTE Confidence: 0.68272287375

00:26:14.766 --> 00:26:17.005 none of them bound to BMP nine and

NOTE Confidence: 0.68272287375

00:26:17.005 --> 00:26:18.705 what stood out about hemogoblin

NOTE Confidence: 0.68272287375

00:26:18.705 --> 00:26:21.647 compared to the other GM's is it had a

NOTE Confidence: 0.68272287375

00:26:21.647 --> 00:26:23.660 relatively higher affinity for the BMP.

NOTE Confidence: 0.68272287375

00:26:23.660 --> 00:26:27.090 567 subfamily compared to the other GM's,

NOTE Confidence: 0.68272287375

00:26:27.090 --> 00:26:29.001 so we thought if there was some

NOTE Confidence: 0.68272287375

00:26:29.001 --> 00:26:30.888 function of human Julian that couldn't

NOTE Confidence: 0.68272287375

00:26:30.888 --> 00:26:32.898 be compensated by the other GM's,

NOTE Confidence: 0.68272287375

00:26:32.900 --> 00:26:33.998 we thought it might have something

NOTE Confidence: 0.68272287375

00:26:33.998 --> 00:26:35.150 to do with the subfamily.

NOTE Confidence: 0.68272287375

00:26:35.150 --> 00:26:38.118 In particular BMP 6.

NOTE Confidence: 0.68272287375

00:26:38.120 --> 00:26:40.976 Another clue came from this experiment,

NOTE Confidence: 0.68272287375

00:26:40.980 --> 00:26:42.807 so here we took mice and we made them

NOTE Confidence: 0.68272287375

00:26:42.807 --> 00:26:44.435 iron deficient by putting them on a

NOTE Confidence: 0.68272287375

00:26:44.435 --> 00:26:46.152 low iron diet or iron overloaded by

NOTE Confidence: 0.68272287375

00:26:46.152 --> 00:26:47.916 putting them on a high iron diet.

NOTE Confidence: 0.68272287375

00:26:47.920 --> 00:26:48.992 And you can see,

NOTE Confidence: 0.68272287375

00:26:48.992 --> 00:26:49.796 as discussed earlier,

NOTE Confidence: 0.68272287375

00:26:49.800 --> 00:26:51.970 the iron deficiency suppresses upside

NOTE Confidence: 0.68272287375

00:26:51.970 --> 00:26:54.939 in and iron overload induces subside in.

NOTE Confidence: 0.68272287375

00:26:54.940 --> 00:26:56.220 So we asked the question,

NOTE Confidence: 0.68272287375

00:26:56.220 --> 00:26:57.724 are any BMP ligands?

NOTE Confidence: 0.68272287375

00:26:57.724 --> 00:26:59.228 Is there expression regulated

NOTE Confidence: 0.68272287375

00:26:59.228 --> 00:27:00.960 by iron and the liver?

NOTE Confidence: 0.68272287375

00:27:00.960 --> 00:27:03.624 And it turns out only two ligands are

NOTE Confidence: 0.68272287375

00:27:03.624 --> 00:27:06.802 one is being P6 reduced by a low iron

NOTE Confidence: 0.68272287375

00:27:06.802 --> 00:27:09.207 diet induced by a high iron diet?

NOTE Confidence: 0.68272287375

00:27:09.210 --> 00:27:11.046 And the other was BMP two,

NOTE Confidence: 0.68272287375

00:27:11.050 --> 00:27:13.246 so these were really good candidate

NOTE Confidence: 0.68272287375

00:27:13.246 --> 00:27:14.710 and dodging US regulators.

NOTE Confidence: 0.68272287375

00:27:14.710 --> 00:27:17.078 But in order so we wanted to validate

NOTE Confidence: 0.68272287375

00:27:17.078 --> 00:27:18.909 this using a genetic approach.

NOTE Confidence: 0.68272287375

00:27:18.910 --> 00:27:20.358 But in order to do this we needed

NOTE Confidence: 0.68272287375

00:27:20.358 --> 00:27:21.775 to know which were the cells

NOTE Confidence: 0.68272287375

00:27:21.775 --> 00:27:23.030 that we're making the ligands,

NOTE Confidence: 0.68272287375

00:27:23.030 --> 00:27:25.046 because the amps are very important

NOTE Confidence: 0.68272287375

00:27:25.046 --> 00:27:26.830 during development and and can

NOTE Confidence: 0.68272287375

00:27:26.830 --> 00:27:28.350 lead to developmental problems.

NOTE Confidence: 0.68272287375

00:27:28.350 --> 00:27:30.206 And so we looked and it turns out

NOTE Confidence: 0.68272287375

00:27:30.206 --> 00:27:32.287 in the liver it's predominantly the

NOTE Confidence: 0.68272287375

00:27:32.287 --> 00:27:34.621 endothelial cells that are making both

NOTE Confidence: 0.68272287375

00:27:34.680 --> 00:27:37.137 the P6 and P and P2 rather than the

NOTE Confidence: 0.68272287375

00:27:37.137 --> 00:27:38.298 parenchymal cells that had ascites,

NOTE Confidence: 0.68272287375

00:27:38.298 --> 00:27:40.019 which are the cells that actually make the.

NOTE Confidence: 0.68272287375

00:27:40.020 --> 00:27:42.990 Side and or the resident tissue

NOTE Confidence: 0.68272287375

00:27:42.990 --> 00:27:44.970 macrophages the Cooper cells.

NOTE Confidence: 0.68272287375

00:27:44.970 --> 00:27:47.031 So we then went on to make a knockout

NOTE Confidence: 0.68272287375

00:27:47.031 --> 00:27:48.722 mice and this is the data for BP

NOTE Confidence: 0.68272287375

00:27:48.722 --> 00:27:50.923 6 and you can see in the both the

NOTE Confidence: 0.68272287375

00:27:50.923 --> 00:27:52.754 the the global knockout is red,

NOTE Confidence: 0.68272287375

00:27:52.754 --> 00:27:54.764 the endothelial knockout is blue,

NOTE Confidence: 0.68272287375

00:27:54.770 --> 00:27:57.829 macrophage is green and hepatocyte is purple.

NOTE Confidence: 0.68272287375

00:27:57.830 --> 00:27:59.606 And what you can see is both a

NOTE Confidence: 0.68272287375

00:27:59.606 --> 00:28:01.189 global and the endothelial BMP.

NOTE Confidence: 0.68272287375

00:28:01.190 --> 00:28:03.005 6 knockout mice had profound

NOTE Confidence: 0.68272287375

00:28:03.005 --> 00:28:04.820 deficiency of hepcidin and this

NOTE Confidence: 0.68272287375

00:28:04.887 --> 00:28:07.359 was associated with all of the

NOTE Confidence: 0.68272287375

00:28:07.359 --> 00:28:09.007 features of hemochromatosis including

NOTE Confidence: 0.68272287375

00:28:09.068 --> 00:28:11.246 massive iron overload and the liver,

NOTE Confidence: 0.68272287375

00:28:11.250 --> 00:28:13.070 which is quantitated here on the left.

NOTE Confidence: 0.68272287375

00:28:13.070 --> 00:28:15.230 Here you can see the global knockout in red.

NOTE Confidence: 0.68272287375

00:28:15.230 --> 00:28:16.850 In the end of the and that kind of

NOTE Confidence: 0.68272287375

00:28:16.850 --> 00:28:18.540 blue and on the right that this is

NOTE Confidence: 0.68272287375

00:28:18.540 --> 00:28:19.958 a Prussian blue stain that stains

NOTE Confidence: 0.68272287375

00:28:19.958 --> 00:28:20.699 the iron blue.

NOTE Confidence: 0.68272287375

00:28:20.700 --> 00:28:22.680 So you can clearly visualize the

NOTE Confidence: 0.68272287375

00:28:22.680 --> 00:28:24.700 massive iron overload in these mice.

NOTE Confidence: 0.68272287375

00:28:24.700 --> 00:28:25.784 For me and B2,

NOTE Confidence: 0.68272287375

00:28:25.784 --> 00:28:27.410 the global knockout mice are embryonic

NOTE Confidence: 0.674513729090909

00:28:27.462 --> 00:28:29.548 lethal, but we did look at endothelial

NOTE Confidence: 0.674513729090909

00:28:29.548 --> 00:28:31.970 BMP 2 knockout mice and similar to BMP 6.

NOTE Confidence: 0.674513729090909

00:28:31.970 --> 00:28:33.685 These mice also had profound

NOTE Confidence: 0.674513729090909

00:28:33.685 --> 00:28:35.400 hepcidin deficiency and all of

NOTE Confidence: 0.674513729090909

00:28:35.459 --> 00:28:37.319 the features of hemochromatosis,

NOTE Confidence: 0.674513729090909

00:28:37.320 --> 00:28:40.578 including iron overload and in fact

NOTE Confidence: 0.674513729090909

00:28:40.580 --> 00:28:42.170 more recent data suggests that BMP

NOTE Confidence: 0.674513729090909

00:28:42.170 --> 00:28:44.116 two and six are actually working

NOTE Confidence: 0.674513729090909

00:28:44.116 --> 00:28:45.776 together to regulate hepcidin.

NOTE Confidence: 0.674513729090909

00:28:45.780 --> 00:28:47.000 It turns out these ligands,

NOTE Confidence: 0.674513729090909

00:28:47.000 --> 00:28:49.214 their dimers, and they can either

NOTE Confidence: 0.674513729090909

00:28:49.214 --> 00:28:51.065 function as as homodimers where

NOTE Confidence: 0.674513729090909

00:28:51.065 --> 00:28:52.938 there's two of the same ligand,

NOTE Confidence: 0.674513729090909

00:28:52.938 --> 00:28:54.370 or heterodimers where they're

NOTE Confidence: 0.674513729090909

00:28:54.370 --> 00:28:55.444 two different ligands.

NOTE Confidence: 0.674513729090909

00:28:55.450 --> 00:28:57.025 And there's an increasing recognition

NOTE Confidence: 0.674513729090909

00:28:57.025 --> 00:28:59.359 in this field that there are some

NOTE Confidence: 0.674513729090909

00:28:59.359 --> 00:29:00.763 biological contexts where only

NOTE Confidence: 0.674513729090909

00:29:00.763 --> 00:29:02.167 heterodimers can function and

NOTE Confidence: 0.674513729090909

00:29:02.221 --> 00:29:03.541 homodimers can't compensate and

NOTE Confidence: 0.674513729090909

00:29:03.541 --> 00:29:05.191 our data suggests that that's

NOTE Confidence: 0.674513729090909

00:29:05.191 --> 00:29:07.630 how BP two and six are working.

NOTE Confidence: 0.674513729090909

00:29:07.630 --> 00:29:09.735 So just to summarize what

NOTE Confidence: 0.674513729090909

00:29:09.735 --> 00:29:11.840 I've shown you so far.

NOTE Confidence: 0.674513729090909

00:29:11.840 --> 00:29:15.615 Iron increases in iron will induce and

NOTE Confidence: 0.674513729090909

00:29:15.615 --> 00:29:17.815 athelia cells in the liver to produce BMP,

NOTE Confidence: 0.674513729090909

00:29:17.820 --> 00:29:19.740 two and BMP 6 ligands.

NOTE Confidence: 0.674513729090909

00:29:19.740 --> 00:29:22.351 These bind to the Coreceptor came a

NOTE Confidence: 0.674513729090909

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00:29:22.351 --> 00:29:24.920 jubilant activate the BMP receptor complex,

NOTE Confidence: 0.674513729090909

00:29:24.920 --> 00:29:27.278 induce the phosphorylation of SMAD proteins,

NOTE Confidence: 0.674513729090909

00:29:27.280 --> 00:29:30.195 which is a major transcriptional

NOTE Confidence: 0.674513729090909

00:29:30.195 --> 00:29:31.944 regulator of hepcidin.

NOTE Confidence: 0.674513729090909

00:29:31.950 --> 00:29:34.002 So now let's switch gears and talk a little

NOTE Confidence: 0.674513729090909

00:29:34.002 --> 00:29:35.830 bit about the erythropoietic signal.

NOTE Confidence: 0.674513729090909

00:29:35.830 --> 00:29:37.335 Now it's been known for a long

NOTE Confidence: 0.674513729090909

00:29:37.335 --> 00:29:38.648 time that whatever the signal is,

NOTE Confidence: 0.674513729090909

00:29:38.650 --> 00:29:40.426 it must be coming from the bone marrow,

NOTE Confidence: 0.674513729090909

00:29:40.430 --> 00:29:42.789 because if you wipe out the bone

NOTE Confidence: 0.674513729090909

00:29:42.789 --> 00:29:44.629 marrow with chemotherapy or radiation,

NOTE Confidence: 0.674513729090909

00:29:44.630 --> 00:29:46.375 and the ability of erythropoietin

NOTE Confidence: 0.674513729090909

00:29:46.375 --> 00:29:48.120 and these other stimulators to

NOTE Confidence: 0.674513729090909

00:29:48.178 --> 00:29:49.868 suppressive side and goes away,

NOTE Confidence: 0.674513729090909

00:29:49.870 --> 00:29:51.695 so it's been hypothesized that

NOTE Confidence: 0.674513729090909

00:29:51.695 --> 00:29:53.947 there must be some secreted factor

NOTE Confidence: 0.674513729090909

00:29:53.947 --> 00:29:56.101 that the bone marrow is making

NOTE Confidence: 0.674513729090909

00:29:56.101 --> 00:29:57.810 that is suppressing hepcidin.

NOTE Confidence: 0.674513729090909

00:29:57.810 --> 00:29:58.986 Several years ago now,

NOTE Confidence: 0.674513729090909

00:29:58.986 --> 00:30:00.750 Tom Ganz's Group discovered one of

NOTE Confidence: 0.674513729090909

00:30:00.807 --> 00:30:02.767 these erythroid regulators of peptide,

NOTE Confidence: 0.674513729090909

00:30:02.770 --> 00:30:05.866 and this is called erythro Faron or Urfi,

NOTE Confidence: 0.674513729090909

00:30:05.870 --> 00:30:07.019 or FAM 132B,

NOTE Confidence: 0.674513729090909

00:30:07.019 --> 00:30:10.310 and this is some data from Toms Group.

NOTE Confidence: 0.674513729090909

00:30:10.310 --> 00:30:12.360 What you can see is if you phlebotomies

NOTE Confidence: 0.674513729090909

00:30:12.360 --> 00:30:14.670 mice or treat them with a report,

NOTE Confidence: 0.674513729090909

00:30:14.670 --> 00:30:16.992 and this causes a robust induction

NOTE Confidence: 0.674513729090909

00:30:16.992 --> 00:30:19.290 of the production of aritha faron

NOTE Confidence: 0.674513729090909

00:30:19.290 --> 00:30:21.642 in the bone marrow by 4 hours,

NOTE Confidence: 0.674513729090909

00:30:21.650 --> 00:30:24.989 which then starts to go down after 15 hours.

NOTE Confidence: 0.674513729090909

00:30:24.990 --> 00:30:26.430 And this is a sort of a mirror

NOTE Confidence: 0.674513729090909

00:30:26.430 --> 00:30:27.807 image of what happens to have.

NOTE Confidence: 0.674513729090909

00:30:27.810 --> 00:30:28.070 Right,

NOTE Confidence: 0.674513729090909

00:30:28.070 --> 00:30:29.890 and so after a referral goes up

NOTE Confidence: 0.674513729090909

00:30:29.890 --> 00:30:31.608 upside and gets suppressed and is

NOTE Confidence: 0.674513729090909

00:30:31.608 --> 00:30:33.324 a referral starts to come down.

NOTE Confidence: 0.674513729090909

00:30:33.330 --> 00:30:34.392 Hepcidin levels rebound.

NOTE Confidence: 0.674513729090909

00:30:34.392 --> 00:30:36.516 And indeed if you inject purified

NOTE Confidence: 0.674513729090909

00:30:36.516 --> 00:30:38.330 it with a ferret into mice,

NOTE Confidence: 0.674513729090909

00:30:38.330 --> 00:30:40.316 it's the prices have sign expression

NOTE Confidence: 0.674513729090909

00:30:40.316 --> 00:30:42.650 and moreover if you look at everything

NOTE Confidence: 0.674513729090909

00:30:42.650 --> 00:30:44.848 fair and knockout mice you know in

NOTE Confidence: 0.674513729090909

00:30:44.909 --> 00:30:47.107 wild type mice where when you give

NOTE Confidence: 0.674513729090909

00:30:47.107 --> 00:30:48.905 them phlebotomy or with points in,

NOTE Confidence: 0.674513729090909

00:30:48.905 --> 00:30:50.900 this will suppress upside and but in

NOTE Confidence: 0.674513729090909

00:30:50.961 --> 00:30:53.418 the earth of Fair knockout mice the

NOTE Confidence: 0.674513729090909

00:30:53.418 --> 00:30:54.970 suppression is significantly blunted,

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NOTE Confidence: 0.674513729090909

00:30:54.970 --> 00:30:56.908 although there is still some suppression,

NOTE Confidence: 0.674513729090909

00:30:56.910 --> 00:30:57.432 suggesting that.

NOTE Confidence: 0.674513729090909

00:30:57.432 --> 00:30:58.998 There are other friend is not

NOTE Confidence: 0.674513729090909

00:30:58.998 --> 00:31:00.520 the only erythroid regulator,

NOTE Confidence: 0.674513729090909

00:31:00.520 --> 00:31:02.501 but certainly it is an important one

NOTE Confidence: 0.674513729090909

00:31:02.501 --> 00:31:04.221 and this is functionally relevant

NOTE Confidence: 0.674513729090909

00:31:04.221 --> 00:31:06.633 because it delays the recovery from

NOTE Confidence: 0.674513729090909

00:31:06.633 --> 00:31:08.679 anemia and these knockout mice.

NOTE Confidence: 0.674513729090909

00:31:08.680 --> 00:31:11.046 And they also showed that this plays

NOTE Confidence: 0.674513729090909

00:31:11.046 --> 00:31:13.374 an important role in the hepcidin

NOTE Confidence: 0.674513729090909

00:31:13.374 --> 00:31:15.876 deficiency in iron overload and thalassemia.

NOTE Confidence: 0.674513729090909

00:31:15.880 --> 00:31:17.650 So our group was interested in

NOTE Confidence: 0.674513729090909

00:31:17.650 --> 00:31:18.830 trying to understand how

NOTE Confidence: 0.763449076666667

00:31:18.892 --> 00:31:20.156 does Erythro Farren work

NOTE Confidence: 0.763449076666667

00:31:20.156 --> 00:31:21.420 to suppress upside in.

NOTE Confidence: 0.763449076666667

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00:31:21.420 --> 00:31:23.124 So we went back to our cell culture

NOTE Confidence: 0.763449076666667

00:31:23.124 --> 00:31:24.736 model and liver cells and you can

NOTE Confidence: 0.763449076666667

00:31:24.736 --> 00:31:26.151 see here that similar to what

NOTE Confidence: 0.763449076666667

00:31:26.151 --> 00:31:27.740 happens in the mice if you treat

NOTE Confidence: 0.763449076666667

00:31:27.740 --> 00:31:29.540 cells with a rifle and protein,

NOTE Confidence: 0.763449076666667

00:31:29.540 --> 00:31:30.880 this will suppressive Sidon.

NOTE Confidence: 0.763449076666667

00:31:30.880 --> 00:31:31.630 And interestingly,

NOTE Confidence: 0.763449076666667

00:31:31.630 --> 00:31:33.880 this also led to a reduction

NOTE Confidence: 0.763449076666667

00:31:33.880 --> 00:31:35.380 in SMAD signaling,

NOTE Confidence: 0.763449076666667

00:31:35.380 --> 00:31:37.696 as evidenced by reduction in the

NOTE Confidence: 0.763449076666667

00:31:37.696 --> 00:31:39.900 phosphorylation of Smad 15 proteins.

NOTE Confidence: 0.763449076666667

00:31:39.900 --> 00:31:42.196 So this suggests that the the way

NOTE Confidence: 0.763449076666667

00:31:42.196 --> 00:31:44.358 Erythro Farren is working is by

NOTE Confidence: 0.763449076666667

00:31:44.358 --> 00:31:46.208 inhibiting the BMP SMAD pathway.

NOTE Confidence: 0.763449076666667

00:31:46.210 --> 00:31:47.535 Now because of whether fairness

NOTE Confidence: 0.763449076666667

00:31:47.535 --> 00:31:48.330 a secreted protein,

00:31:48.330 --> 00:31:50.388 we reasoned it might be interacting

00:31:50.388 --> 00:31:52.522 directly with BMP ligands or receptors

00:31:52.522 --> 00:31:54.287 to interfere with this pathway.

00:31:54.290 --> 00:31:57.286 And so we tested that using a

00:31:57.286 --> 00:31:58.142 coimmunoprecipitation approach.

00:31:58.150 --> 00:32:00.302 So here what we did is we mixed

00:32:00.302 --> 00:32:01.849 BMP ligands and a flag tag.

00:32:01.850 --> 00:32:03.608 The with warfarin together and this

00:32:03.608 --> 00:32:06.010 here is a BMP 26 heterodimeric Lagann

00:32:06.010 --> 00:32:08.830 and here is BMP 6 homodimeric ligand.

00:32:08.830 --> 00:32:10.286 We we immunoprecipitated erythroxylum

00:32:10.286 --> 00:32:12.773 with a flag antibody and you can

00:32:12.773 --> 00:32:14.261 see that the ligand comes down

00:32:14.261 --> 00:32:16.328 with it so this demonstrates that.

00:32:16.330 --> 00:32:18.202 Both are fair and is actually

00:32:18.202 --> 00:32:20.219 binding directly to the BMP ligands.

NOTE Confidence: 0.763449076666667

00:32:20.220 --> 00:32:21.128 In contrast,

NOTE Confidence: 0.763449076666667

00:32:21.128 --> 00:32:23.852 there is no interaction between over

NOTE Confidence: 0.763449076666667

00:32:23.852 --> 00:32:26.569 the farm and the BMP receptors.

NOTE Confidence: 0.763449076666667

00:32:26.570 --> 00:32:28.355 So the way we think this is

NOTE Confidence: 0.763449076666667

00:32:28.355 --> 00:32:30.173 working is illustrated by this

NOTE Confidence: 0.763449076666667

00:32:30.173 --> 00:32:31.169 immunoprecipitation experiment.

NOTE Confidence: 0.763449076666667

00:32:31.170 --> 00:32:33.771 So here what we do is we're mixing together

NOTE Confidence: 0.763449076666667

00:32:33.771 --> 00:32:36.149 the BMP ligand and the BMP receptors.

NOTE Confidence: 0.763449076666667

00:32:36.150 --> 00:32:39.188 So if you immuno precipitate the receptor,

NOTE Confidence: 0.763449076666667

00:32:39.190 --> 00:32:40.380 the ligand comes down with

NOTE Confidence: 0.763449076666667

00:32:40.380 --> 00:32:41.570 it as you would expect,

NOTE Confidence: 0.763449076666667

00:32:41.570 --> 00:32:43.430 the ligand binds to the receptor.

NOTE Confidence: 0.763449076666667

00:32:43.430 --> 00:32:46.103 But this is in the absence of Aritha Faron.

NOTE Confidence: 0.763449076666667

00:32:46.110 --> 00:32:47.342 When you add increasing

NOTE Confidence: 0.763449076666667

00:32:47.342 --> 00:32:48.882 Aritha Faron to this mixture,

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NOTE Confidence: 0.763449076666667

00:32:48.890 --> 00:32:51.346 what happens is you compete for the ability

NOTE Confidence: 0.763449076666667

00:32:51.346 --> 00:32:53.927 of the ligand to bind to the receptor.

NOTE Confidence: 0.763449076666667

00:32:53.930 --> 00:32:55.610 So this suggests that the way with

NOTE Confidence: 0.763449076666667

00:32:55.610 --> 00:32:56.730 referring is working is like.

NOTE Confidence: 0.763449076666667

00:32:56.730 --> 00:32:57.360 Ligand trek,

NOTE Confidence: 0.763449076666667

00:32:57.360 --> 00:32:59.250 it binds the ligands and sequesters

NOTE Confidence: 0.763449076666667

00:32:59.250 --> 00:33:01.517 it and prevents it from interacting

NOTE Confidence: 0.763449076666667

00:33:01.517 --> 00:33:02.696 with the receptors,

NOTE Confidence: 0.763449076666667

00:33:02.700 --> 00:33:05.538 thereby inhibiting signaling.

NOTE Confidence: 0.763449076666667

00:33:05.540 --> 00:33:05.793 So,

NOTE Confidence: 0.763449076666667

00:33:05.793 --> 00:33:06.552 just to summarize,

NOTE Confidence: 0.763449076666667

00:33:06.552 --> 00:33:07.817 this part of the talk,

NOTE Confidence: 0.763449076666667

00:33:07.820 --> 00:33:10.196 here's the the canonical BMP signaling

NOTE Confidence: 0.763449076666667

00:33:10.196 --> 00:33:12.340 pathway that we discussed earlier,

NOTE Confidence: 0.763449076666667

00:33:12.340 --> 00:33:14.488 and Othello cells make BMP ligands

NOTE Confidence: 0.763449076666667

00:33:14.488 --> 00:33:16.907 which bind to the BMP receptor

NOTE Confidence: 0.763449076666667

00:33:16.907 --> 00:33:19.202 complex to induce the transcription

NOTE Confidence: 0.763449076666667

00:33:19.202 --> 00:33:21.310 of hepcidin in the context of Earth,

NOTE Confidence: 0.763449076666667

00:33:21.310 --> 00:33:24.397 reported drive like EPO injections or anemia.

NOTE Confidence: 0.763449076666667

00:33:24.400 --> 00:33:26.600 This acts on the kidney to induce the

NOTE Confidence: 0.763449076666667

00:33:26.600 --> 00:33:27.827 production of erythropoietin which

NOTE Confidence: 0.763449076666667

00:33:27.827 --> 00:33:30.011 acts on the bone marrow to induce

NOTE Confidence: 0.763449076666667

00:33:30.011 --> 00:33:31.840 the production of Arthur Farum,

NOTE Confidence: 0.763449076666667

00:33:31.840 --> 00:33:34.228 which then goes to the liver

NOTE Confidence: 0.763449076666667

00:33:34.228 --> 00:33:35.820 where spines and sequesters.

NOTE Confidence: 0.763449076666667

00:33:35.820 --> 00:33:37.704 BMP ligands inhibit signaling

NOTE Confidence: 0.763449076666667

00:33:37.704 --> 00:33:39.117 through this pathway,

NOTE Confidence: 0.763449076666667

00:33:39.120 --> 00:33:42.580 thereby lowering hepcidin expression.

NOTE Confidence: 0.763449076666667

00:33:42.580 --> 00:33:43.176 So finally,

NOTE Confidence: 0.763449076666667

00:33:43.176 --> 00:33:45.262 let's talk a little bit about inflammation.

NOTE Confidence: 0.763449076666667

00:33:45.270 --> 00:33:46.698 You know we mentioned this is

NOTE Confidence: 0.763449076666667

00:33:46.698 --> 00:33:48.265 probably one of the the mechanisms

NOTE Confidence: 0.763449076666667

00:33:48.265 --> 00:33:49.957 by which have sided is increased

NOTE Confidence: 0.763449076666667

00:33:49.957 --> 00:33:51.299 in chronic kidney disease.

NOTE Confidence: 0.763449076666667

00:33:51.300 --> 00:33:53.418 So how does inflammation regulate herbicide?

NOTE Confidence: 0.763449076666667

00:33:53.420 --> 00:33:55.548 And so this was illustrated by a

NOTE Confidence: 0.763449076666667

00:33:55.548 --> 00:33:57.210 number of different groups that

NOTE Confidence: 0.763449076666667

00:33:57.210 --> 00:33:58.590 inflammatory cytokines such as

NOTE Confidence: 0.763449076666667

00:33:58.590 --> 00:34:01.292 aisle 6 will act through the Jack

NOTE Confidence: 0.763449076666667

00:34:01.292 --> 00:34:03.397 stat pathway through a direct

NOTE Confidence: 0.763449076666667

00:34:03.397 --> 00:34:04.594 transcriptional mechanism through

NOTE Confidence: 0.763449076666667

00:34:04.594 --> 00:34:06.718 a stat binding element on the

NOTE Confidence: 0.763449076666667

00:34:06.718 --> 00:34:07.780 herbicide and promoter.

NOTE Confidence: 0.763449076666667

00:34:07.780 --> 00:34:08.111 Now,

NOTE Confidence: 0.763449076666667

00:34:08.111 --> 00:34:09.766 although this is a distinct

NOTE Confidence: 0.763449076666667

00:34:09.766 --> 00:34:11.090 pathway from the BMP

NOTE Confidence: 0.802749805833333

00:34:11.157 --> 00:34:13.620 SMAD pathway. It still turns out that

NOTE Confidence: 0.802749805833333

00:34:13.620 --> 00:34:16.230 this being piece Med pathway is important

NOTE Confidence: 0.802749805833333

00:34:16.230 --> 00:34:18.870 for the inflammatory reaction to occur,

NOTE Confidence: 0.802749805833333

00:34:18.870 --> 00:34:21.450 and that's illustrated in this experiment.

NOTE Confidence: 0.802749805833333

00:34:21.450 --> 00:34:23.482 So what we did is we made mice

NOTE Confidence: 0.802749805833333

00:34:23.482 --> 00:34:25.419 where we knocked out the smed

NOTE Confidence: 0.802749805833333

00:34:25.419 --> 00:34:27.453 1/5 and eight in the parasites,

NOTE Confidence: 0.802749805833333

00:34:27.460 --> 00:34:28.670 and as you might expect,

NOTE Confidence: 0.802749805833333

00:34:28.670 --> 00:34:30.655 these mice have a profound

NOTE Confidence: 0.802749805833333

00:34:30.655 --> 00:34:31.846 have signed deficiency.

NOTE Confidence: 0.802749805833333

00:34:31.850 --> 00:34:34.690 Kind of like the BMP ligand knockout mice,

NOTE Confidence: 0.802749805833333

00:34:34.690 --> 00:34:37.224 and compared to the the control mice.

NOTE Confidence: 0.802749805833333

00:34:37.230 --> 00:34:40.016 Now if we treat these mice with

NOTE Confidence: 0.802749805833333

00:34:40.016 --> 00:34:42.140 lipopolysaccharide to induce inflammation.

NOTE Confidence: 0.802749805833333

00:34:42.140 --> 00:34:44.639 Hepcidin is actually induced both in the

NOTE Confidence: 0.802749805833333

00:34:44.639 --> 00:34:47.313 knockout mice and in the wild type mice

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NOTE Confidence: 0.802749805833333

00:34:47.313 --> 00:34:49.530 because this aisle 6 pathway is intact,

NOTE Confidence: 0.802749805833333

00:34:49.530 --> 00:34:51.474 but because pepsin levels start out

NOTE Confidence: 0.802749805833333

00:34:51.474 --> 00:34:53.959 so much lower in the knockout mice,

NOTE Confidence: 0.802749805833333

00:34:53.960 --> 00:34:56.445 the ending helpside values are still much

NOTE Confidence: 0.802749805833333

00:34:56.445 --> 00:34:59.134 lower in this man knockout mice because

NOTE Confidence: 0.802749805833333

00:34:59.134 --> 00:35:01.980 of the reduction in basil hepcidin levels,

NOTE Confidence: 0.802749805833333

00:35:01.980 --> 00:35:04.080 so this suggests that one could

NOTE Confidence: 0.802749805833333

00:35:04.080 --> 00:35:05.775 actually think about targeting any

NOTE Confidence: 0.802749805833333

00:35:05.775 --> 00:35:07.840 of these molecular pathways as as as

NOTE Confidence: 0.802749805833333

00:35:07.840 --> 00:35:09.902 a strategy to think about lowering

NOTE Confidence: 0.802749805833333

00:35:09.902 --> 00:35:12.020 upside and in chronic kidney disease.

NOTE Confidence: 0.802749805833333

00:35:12.020 --> 00:35:13.532 Questions and a number of groups

NOTE Confidence: 0.802749805833333

00:35:13.532 --> 00:35:15.270 have done a number of these things

NOTE Confidence: 0.802749805833333

00:35:15.270 --> 00:35:17.133 and I'm just going to show you a

NOTE Confidence: 0.802749805833333

00:35:17.133 --> 00:35:18.687 little bit of data from our group.

NOTE Confidence: 0.802749805833333

00:35:18.690 --> 00:35:21.161 So the first strategy that we thought

NOTE Confidence: 0.802749805833333

00:35:21.161 --> 00:35:22.951 about was something was making

NOTE Confidence: 0.802749805833333

00:35:22.951 --> 00:35:24.949 a soluble form of human javelin.

NOTE Confidence: 0.802749805833333

00:35:24.950 --> 00:35:26.638 So here what we do is we replace

NOTE Confidence: 0.802749805833333

00:35:26.638 --> 00:35:28.378 the GPI anchor that anchors him.

NOTE Confidence: 0.802749805833333

00:35:28.380 --> 00:35:30.036 The jubilant to the membrane surface,

NOTE Confidence: 0.802749805833333

00:35:30.040 --> 00:35:32.861 and we replace it with an FC

NOTE Confidence: 0.802749805833333

00:35:32.861 --> 00:35:34.070 tail from immunoglobulin.

NOTE Confidence: 0.802749805833333

00:35:34.070 --> 00:35:36.352 The idea being kind of like erythroxylum

NOTE Confidence: 0.802749805833333

00:35:36.352 --> 00:35:38.190 because it binds to the ligand,

NOTE Confidence: 0.802749805833333

00:35:38.190 --> 00:35:39.565 but it's not associated anymore

NOTE Confidence: 0.802749805833333

00:35:39.565 --> 00:35:40.665 with the cell surface.

NOTE Confidence: 0.802749805833333

00:35:40.670 --> 00:35:42.574 It may act as a ligand track.

NOTE Confidence: 0.802749805833333

00:35:42.580 --> 00:35:44.470 And the beauty of this type of

NOTE Confidence: 0.802749805833333

00:35:44.470 --> 00:35:46.543 strategy is we were able to design

NOTE Confidence: 0.802749805833333

00:35:46.543 --> 00:35:48.863 this even before we knew which were

NOTE Confidence: 0.802749805833333

00:35:48.863 --> 00:35:50.687 the important endogenous ligands.

NOTE Confidence: 0.802749805833333

00:35:50.690 --> 00:35:52.419 We reasoned that whatever those ligands are,

NOTE Confidence: 0.802749805833333

00:35:52.420 --> 00:35:54.538 they must bind to human Julian

NOTE Confidence: 0.802749805833333

00:35:54.538 --> 00:35:56.560 because it's the endogenous receptor.

NOTE Confidence: 0.802749805833333

00:35:56.560 --> 00:35:57.148 Subsequently,

NOTE Confidence: 0.802749805833333

00:35:57.148 --> 00:36:00.676 we also developed a BMP 6

NOTE Confidence: 0.802749805833333

00:36:00.676 --> 00:36:02.440 neutralizing antibody strategy.

NOTE Confidence: 0.802749805833333

00:36:02.440 --> 00:36:05.170 Once we identified BMP six as

NOTE Confidence: 0.802749805833333

00:36:05.170 --> 00:36:06.812 an important endogenous ligand.

NOTE Confidence: 0.802749805833333

00:36:06.812 --> 00:36:09.374 So here's a little bit of data.

NOTE Confidence: 0.802749805833333

00:36:09.380 --> 00:36:11.348 This was done in collaboration with

NOTE Confidence: 0.802749805833333

00:36:11.348 --> 00:36:13.050 Igor thorough and Doctor Weiss.

NOTE Confidence: 0.802749805833333

00:36:13.050 --> 00:36:15.540 This is in a rat model of any of the

NOTE Confidence: 0.802749805833333

00:36:15.612 --> 00:36:17.997 information induced by injection of

NOTE Confidence: 0.802749805833333

00:36:17.997 --> 00:36:20.382 peptidoglycan from Group A strep.

NOTE Confidence: 0.802749805833333

00:36:20.390 --> 00:36:21.728 When you inject this into mice,

NOTE Confidence: 0.802749805833333

00:36:21.730 --> 00:36:22.900 they get a chronic relapsing

NOTE Confidence: 0.802749805833333

00:36:22.900 --> 00:36:24.423 arthritis with all of the features

NOTE Confidence: 0.802749805833333

00:36:24.423 --> 00:36:25.639 of anemia of inflammation,

NOTE Confidence: 0.802749805833333

00:36:25.640 --> 00:36:26.804 including high peptide levels.

NOTE Confidence: 0.802749805833333

00:36:26.804 --> 00:36:29.179 So what you can see here is that

NOTE Confidence: 0.802749805833333

00:36:29.179 --> 00:36:30.895 the rats treated with the soluble

NOTE Confidence: 0.802749805833333

00:36:30.895 --> 00:36:32.922 human Julian had at least a trend

NOTE Confidence: 0.802749805833333

00:36:32.922 --> 00:36:34.322 toward a reduction and hepcidin,

NOTE Confidence: 0.802749805833333

00:36:34.330 --> 00:36:36.070 although that didn't quite reach

NOTE Confidence: 0.802749805833333

00:36:36.070 --> 00:36:37.810 statistical significance in this study,

NOTE Confidence: 0.802749805833333

00:36:37.810 --> 00:36:40.222 but it was enough to stabilize

NOTE Confidence: 0.802749805833333

00:36:40.222 --> 00:36:42.236 Fairport and protein expression and

NOTE Confidence: 0.802749805833333

00:36:42.236 --> 00:36:44.240 mobilize iron out of the stores.

NOTE Confidence: 0.802749805833333

00:36:44.240 --> 00:36:46.496 Into the the blood and importantly,

NOTE Confidence: 0.802749805833333

00:36:46.500 --> 00:36:48.726 it was able to improve anemia.

NOTE Confidence: 0.658735201666667

00:36:51.450 --> 00:36:53.823 Similar data we're also shown what the

NOTE Confidence: 0.658735201666667

00:36:53.823 --> 00:36:56.092 neutralizing the MP six antibody now,

NOTE Confidence: 0.658735201666667

00:36:56.092 --> 00:36:58.984 interestingly, as a study was published

NOTE Confidence: 0.658735201666667

00:36:58.990 --> 00:37:01.216 recently where they did a first in

NOTE Confidence: 0.658735201666667

00:37:01.216 --> 00:37:03.479 human trial for the neutralizing BMP 6

NOTE Confidence: 0.658735201666667

00:37:03.479 --> 00:37:05.990 antibody as a way to lower hepcidin.

NOTE Confidence: 0.658735201666667

00:37:05.990 --> 00:37:08.284 Anemia of chronic kidney disease. Now,

NOTE Confidence: 0.658735201666667

00:37:08.284 --> 00:37:11.290 as as I'm sure most of this audience knows,

NOTE Confidence: 0.658735201666667

00:37:11.290 --> 00:37:13.243 in phase one trials, the purpose of

NOTE Confidence: 0.658735201666667

00:37:13.243 --> 00:37:15.370 the trial is to look for toxicity.

NOTE Confidence: 0.658735201666667

00:37:15.370 --> 00:37:16.342 A dose finding right?

NOTE Confidence: 0.658735201666667

00:37:16.342 --> 00:37:17.314 It's not an efficacy.

NOTE Confidence: 0.658735201666667

00:37:17.320 --> 00:37:19.398 It's not designed as an efficacy trial, but.

NOTE Confidence: 0.658735201666667

00:37:19.398 --> 00:37:21.414 At times people of course do measure

NOTE Confidence: 0.658735201666667

00:37:21.414 --> 00:37:23.194 some efficacy and points to get some

NOTE Confidence: 0.658735201666667

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00:37:23.194 --> 00:37:25.184 hints if if your drug might be doing

NOTE Confidence: 0.658735201666667

00:37:25.184 --> 00:37:27.011 what you think it's supposed to do,

NOTE Confidence: 0.658735201666667

00:37:27.020 --> 00:37:28.900 and that's what they did in the study.

NOTE Confidence: 0.658735201666667

00:37:28.900 --> 00:37:30.846 So here these are all in kidney

NOTE Confidence: 0.658735201666667

00:37:30.846 --> 00:37:32.594 disease patients and they the red

NOTE Confidence: 0.658735201666667

00:37:32.594 --> 00:37:34.014 triangles show patients who got

NOTE Confidence: 0.658735201666667

00:37:34.014 --> 00:37:36.137 one dose of the neutralizing BMP 6

NOTE Confidence: 0.658735201666667

00:37:36.137 --> 00:37:38.306 antibody and the black circles are the

NOTE Confidence: 0.658735201666667

00:37:38.306 --> 00:37:40.304 control and they didn't provide any

NOTE Confidence: 0.658735201666667

00:37:40.304 --> 00:37:41.698 statistical analysis in the study.

NOTE Confidence: 0.658735201666667

00:37:41.700 --> 00:37:43.324 And again I'm sure it was underpowered

NOTE Confidence: 0.658735201666667

00:37:43.324 --> 00:37:45.258 to look at these efficacy endpoints,

NOTE Confidence: 0.658735201666667

00:37:45.260 --> 00:37:47.017 but what you can see here intriguingly

NOTE Confidence: 0.658735201666667

00:37:47.017 --> 00:37:48.798 is that the neutralizing the MP

NOTE Confidence: 0.658735201666667

00:37:48.798 --> 00:37:50.428 six antibodies seem to suppress.

NOTE Confidence: 0.658735201666667

00:37:50.430 --> 00:37:52.929 Side and levels.

NOTE Confidence: 0.658735201666667

00:37:52.930 --> 00:37:53.632 Lowered ferritin,

NOTE Confidence: 0.658735201666667

00:37:53.632 --> 00:37:56.089 so ferritin is the iron storage protein,

NOTE Confidence: 0.658735201666667

00:37:56.090 --> 00:37:57.962 so this suggests that iron is

NOTE Confidence: 0.658735201666667

00:37:57.962 --> 00:37:59.930 being mobilized out of the stores,

NOTE Confidence: 0.658735201666667

00:37:59.930 --> 00:38:01.226 increased serum iron levels,

NOTE Confidence: 0.658735201666667

00:38:01.226 --> 00:38:03.665 and actually at least cause a tendency

NOTE Confidence: 0.658735201666667

00:38:03.665 --> 00:38:05.409 to increase hemoglobin levels.

NOTE Confidence: 0.658735201666667

00:38:05.410 --> 00:38:08.161 So kind of intriguing hints that that

NOTE Confidence: 0.658735201666667

00:38:08.161 --> 00:38:11.787 there may be a clinical possibilities here,

NOTE Confidence: 0.658735201666667

00:38:11.790 --> 00:38:13.426 and so you know,

NOTE Confidence: 0.658735201666667

00:38:13.426 --> 00:38:15.062 understanding all these molecular

NOTE Confidence: 0.658735201666667

00:38:15.062 --> 00:38:16.990 pathways has LED not only us,

NOTE Confidence: 0.658735201666667

00:38:16.990 --> 00:38:18.831 but a number of different groups to

NOTE Confidence: 0.658735201666667

00:38:18.831 --> 00:38:20.206 think about targeting these pathways

NOTE Confidence: 0.658735201666667

00:38:20.206 --> 00:38:22.387 as a strategy. And people have.

NOTE Confidence: 0.658735201666667

00:38:22.387 --> 00:38:24.223 Targeted everything from hepcidin

NOTE Confidence: 0.658735201666667

00:38:24.223 --> 00:38:26.768 and Fairport and directly to BMP.

NOTE Confidence: 0.658735201666667

00:38:26.770 --> 00:38:28.674 6 logins to him.

NOTE Confidence: 0.658735201666667

00:38:28.674 --> 00:38:31.054 Adjuvant coreceptor to BMP receptors,

NOTE Confidence: 0.658735201666667

00:38:31.060 --> 00:38:32.836 SMAD proteins and also the aisle.

NOTE Confidence: 0.658735201666667

00:38:32.840 --> 00:38:34.432 6 stat. 3 pathway.

NOTE Confidence: 0.658735201666667

00:38:34.432 --> 00:38:36.820 All of these strategies are actually

NOTE Confidence: 0.658735201666667

00:38:36.894 --> 00:38:39.477 shown benefit in animal models and a

NOTE Confidence: 0.658735201666667

00:38:39.477 --> 00:38:42.027 number of them have actually advanced

NOTE Confidence: 0.658735201666667

00:38:42.027 --> 00:38:45.219 to various stages of of clinical trials.

NOTE Confidence: 0.658735201666667

00:38:45.220 --> 00:38:45.854 So finally,

NOTE Confidence: 0.658735201666667

00:38:45.854 --> 00:38:47.756 I'll just conclude with the saying

NOTE Confidence: 0.658735201666667

00:38:47.756 --> 00:38:49.742 that that I hope I've convinced

NOTE Confidence: 0.658735201666667

00:38:49.742 --> 00:38:51.680 you that there's been a revolution,

NOTE Confidence: 0.658735201666667

00:38:51.680 --> 00:38:53.625 and our molecular understanding of

NOTE Confidence: 0.658735201666667

00:38:53.625 --> 00:38:55.181 systemic iron homeostasis regulation

NOTE Confidence: 0.658735201666667

00:38:55.181 --> 00:38:57.439 and the pathogenesis of iron disorders,

NOTE Confidence: 0.658735201666667

00:38:57.440 --> 00:39:00.180 including anemia, chronic kidney disease,

NOTE Confidence: 0.658735201666667

00:39:00.180 --> 00:39:02.630 and these findings hold the promise for

NOTE Confidence: 0.658735201666667

00:39:02.630 --> 00:39:04.798 more targeted therapies for iron disorders,

NOTE Confidence: 0.658735201666667

00:39:04.800 --> 00:39:06.040 particularly for kidney disease.

NOTE Confidence: 0.658735201666667

00:39:06.040 --> 00:39:06.970 Patients have signed.

NOTE Confidence: 0.658735201666667

00:39:06.970 --> 00:39:09.100 This elevates that in these patients

NOTE Confidence: 0.658735201666667

00:39:09.100 --> 00:39:11.024 and contributes to iron restricted

NOTE Confidence: 0.658735201666667

00:39:11.024 --> 00:39:13.146 with poisonous and anemia, peptide,

NOTE Confidence: 0.658735201666667

00:39:13.146 --> 00:39:14.976 and fairpoint and access modulators.

NOTE Confidence: 0.658735201666667

00:39:14.980 --> 00:39:16.604 May have a role in treating anemia,

NOTE Confidence: 0.658735201666667

00:39:16.610 --> 00:39:18.992 CKD by increasing iron availability from

NOTE Confidence: 0.658735201666667

00:39:18.992 --> 00:39:22.230 the diet and from the patient's own body.

NOTE Confidence: 0.658735201666667

00:39:22.230 --> 00:39:25.068 Stores and studies are ongoing to

NOTE Confidence: 0.658735201666667

00:39:25.068 --> 00:39:28.086 determine efficacy and safety of these

NOTE Confidence: 0.658735201666667

00:39:28.086 --> 00:39:30.186 strategies in inpatient patients.

NOTE Confidence: 0.658735201666667

00:39:30.190 --> 00:39:31.782 I'll just end by thanking the folks in

NOTE Confidence: 0.658735201666667

00:39:31.782 --> 00:39:33.688 my lab and our collaborators around the

NOTE Confidence: 0.658735201666667

00:39:33.688 --> 00:39:35.550 world who've contributed to these studies,

NOTE Confidence: 0.658735201666667

00:39:35.550 --> 00:39:37.426 as well as our funding sources and

NOTE Confidence: 0.658735201666667

00:39:37.426 --> 00:39:39.049 thank everyone for your attention,

NOTE Confidence: 0.658735201666667

00:39:39.050 --> 00:39:41.106 and I'll be happy to answer any questions.

NOTE Confidence: 0.5741738

00:39:51.630 --> 00:39:55.120 Sure. That was a lovely talk

NOTE Confidence: 0.5741738

00:39:55.120 --> 00:39:57.838 couple of questions like my so.

NOTE Confidence: 0.5741738

00:39:57.840 --> 00:39:59.786 So first of all, it sounds like

NOTE Confidence: 0.5741738

00:39:59.786 --> 00:40:01.525 the iron sensor governing the

NOTE Confidence: 0.5741738

00:40:01.525 --> 00:40:03.635 production side really designed for.

NOTE Confidence: 0.919158825

00:40:05.990 --> 00:40:09.020 So this it's actually more complicated

NOTE Confidence: 0.919158825

00:40:09.020 --> 00:40:10.818 than that, so it turns out that there's

NOTE Confidence: 0.919158825

00:40:10.818 --> 00:40:12.230 two different kinds of iron signals.

NOTE Confidence: 0.919158825

00:40:12.230 --> 00:40:13.438 There's the stores signal

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NOTE Confidence: 0.919158825

00:40:13.438 --> 00:40:14.646 that's kind of reflective.

NOTE Confidence: 0.919158825

00:40:14.650 --> 00:40:15.742 The total body stores,

NOTE Confidence: 0.919158825

00:40:15.742 --> 00:40:17.774 and that signal we think is coming

NOTE Confidence: 0.919158825

00:40:17.774 --> 00:40:19.784 from the endothelial cells and data.

NOTE Confidence: 0.919158825

00:40:19.790 --> 00:40:22.166 I didn't have time to show you today.

NOTE Confidence: 0.919158825

00:40:22.170 --> 00:40:24.088 We and other groups have worked out

NOTE Confidence: 0.919158825

00:40:24.088 --> 00:40:26.375 that one of the mechanisms is that

NOTE Confidence: 0.919158825

00:40:26.375 --> 00:40:28.125 iron induces oxidative stress and

NOTE Confidence: 0.919158825

00:40:28.125 --> 00:40:30.410 NRF 2 pathway and endothelial cells.

NOTE Confidence: 0.919158825

00:40:30.410 --> 00:40:32.140 And this is actually a

NOTE Confidence: 0.919158825

00:40:32.140 --> 00:40:33.524 transcriptional regulator of B6.

NOTE Confidence: 0.919158825

00:40:33.530 --> 00:40:35.038 So that's one pathway.

NOTE Confidence: 0.919158825

00:40:35.038 --> 00:40:37.747 But it turns out that circulating iron

NOTE Confidence: 0.919158825

00:40:37.747 --> 00:40:39.997 levels actually seem to be sensed.

NOTE Confidence: 0.919158825

00:40:40.000 --> 00:40:42.718 We think directly in the hepatocytes

NOTE Confidence: 0.919158825

00:40:42.718 --> 00:40:44.077 via transparent receptors,

NOTE Confidence: 0.919158825

00:40:44.080 --> 00:40:46.060 so there's two different transparent

NOTE Confidence: 0.919158825

00:40:46.060 --> 00:40:48.040 receptors in the liver transparent

NOTE Confidence: 0.919158825

00:40:48.098 --> 00:40:50.474 receptor 2 which is mutated in

NOTE Confidence: 0.919158825

00:40:50.474 --> 00:40:51.662 hemochromatosis and transparent

NOTE Confidence: 0.919158825

00:40:51.662 --> 00:40:53.957 receptor one which actually binds to

NOTE Confidence: 0.919158825

00:40:53.957 --> 00:40:55.797 the other hemochromatosis protein HFV.

NOTE Confidence: 0.919158825

00:40:55.800 --> 00:40:58.089 And when circulating iron levels go up,

NOTE Confidence: 0.919158825

00:40:58.090 --> 00:41:00.925 it's sensed by those proteins and and

NOTE Confidence: 0.919158825

00:41:00.925 --> 00:41:03.588 somehow that causes HF and transparent

NOTE Confidence: 0.919158825

00:41:03.588 --> 00:41:05.898 receptor 2 to regulate hepcidin.

NOTE Confidence: 0.919158825

00:41:05.900 --> 00:41:07.670 So it's actually a complex I.

NOTE Confidence: 0.919158825

00:41:07.670 --> 00:41:09.038 I simplified it here and and

NOTE Confidence: 0.919158825

00:41:09.038 --> 00:41:10.709 focused on one part of the pathway,

NOTE Confidence: 0.919158825

00:41:10.710 --> 00:41:12.240 but there's probably multiple signals.

NOTE Confidence: 0.686870208333333

00:41:14.870 --> 00:41:18.990 Have some items on the 25. Please.

NOTE Confidence: 0.700318063333333

00:41:21.120 --> 00:41:23.229 What's the biology?

NOTE Confidence: 0.700318063333333

00:41:23.230 --> 00:41:25.456 Yes, so it is cleaved at.

NOTE Confidence: 0.700318063333333

00:41:25.460 --> 00:41:27.416 It's cleaved by Furin and furin.

NOTE Confidence: 0.700318063333333

00:41:27.420 --> 00:41:28.610 Like proteins.

NOTE Confidence: 0.700318063333333

00:41:28.610 --> 00:41:30.990 There isn't any people.

NOTE Confidence: 0.700318063333333

00:41:30.990 --> 00:41:33.699 Have looked at the Pro, the pro hormone.

NOTE Confidence: 0.700318063333333

00:41:33.699 --> 00:41:35.817 It doesn't have a biological function

NOTE Confidence: 0.700318063333333

00:41:35.817 --> 00:41:38.718 as far as we know and there's no clear

NOTE Confidence: 0.700318063333333

00:41:38.718 --> 00:41:40.889 known function of the cleavage project.

NOTE Confidence: 0.700318063333333

00:41:40.890 --> 00:41:42.510 The end terminal cleavage,

NOTE Confidence: 0.700318063333333

00:41:42.510 --> 00:41:44.130 the other cleavage products

NOTE Confidence: 0.700318063333333

00:41:44.130 --> 00:41:45.520 that have sighted.

NOTE Confidence: 0.700318063333333

00:41:45.520 --> 00:41:46.810 That's all we know right now.

NOTE Confidence: 0.763553722577778

00:42:02.440 --> 00:42:04.764 Yeah, so hepcidin turns out this turned

NOTE Confidence: 0.763553722577778

00:42:04.764 --> 00:42:06.633 over really quickly and that's been

NOTE Confidence: 0.763553722577778

00:42:06.633 --> 00:42:08.907 I think one of the the downsides of

NOTE Confidence: 0.763553722577778

00:42:08.907 --> 00:42:10.839 trying to target upside and directly.

NOTE Confidence: 0.763553722577778

00:42:10.840 --> 00:42:12.360 So obviously that was one of the first

NOTE Confidence: 0.763553722577778

00:42:12.360 --> 00:42:13.660 things that people tried to target,

NOTE Confidence: 0.763553722577778

00:42:13.660 --> 00:42:16.796 but I think that's one of the limitations

NOTE Confidence: 0.763553722577778

00:42:16.796 --> 00:42:18.592 of targeting peptide and protein directly.

NOTE Confidence: 0.763553722577778

00:42:18.592 --> 00:42:20.660 I don't have the numbers on the top of

NOTE Confidence: 0.763553722577778

00:42:20.660 --> 00:42:22.370 my head, but it's very fast. Server.

NOTE Confidence: 0.888243302857143

00:42:24.980 --> 00:42:27.395 I don't know that it's fully understood.

NOTE Confidence: 0.888243302857143

00:42:27.400 --> 00:42:29.296 It's there's some evidence that suggests

NOTE Confidence: 0.888243302857143

00:42:29.296 --> 00:42:32.117 that it could be taken up in the the

NOTE Confidence: 0.888243302857143

00:42:32.117 --> 00:42:34.010 proximal tubule and maybe degraded there,

NOTE Confidence: 0.888243302857143

00:42:34.010 --> 00:42:36.110 but I don't know that people have

NOTE Confidence: 0.888243302857143

00:42:36.110 --> 00:42:38.090 fully worked out how that happens.

NOTE Confidence: 0.663728835076923

00:42:42.670 --> 00:42:44.746 Do you think that transferring and

NOTE Confidence: 0.663728835076923

00:42:44.746 --> 00:42:47.288 ferritin are still the things to measure?

NOTE Confidence: 0.663728835076923

00:42:47.290 --> 00:42:49.684 Are there other modalities that that

NOTE Confidence: 0.663728835076923

00:42:49.684 --> 00:42:51.880 we seem like since, like training?

NOTE Confidence: 0.93397822

00:42:53.900 --> 00:42:55.258 Yeah, I think that's a great question.

NOTE Confidence: 0.93397822

00:42:55.260 --> 00:42:57.555 I think they're definitely limitations

NOTE Confidence: 0.93397822

00:42:57.555 --> 00:43:00.519 of the the the measures we have.

NOTE Confidence: 0.93397822

00:43:00.520 --> 00:43:01.864 You know, particularly ferritin,

NOTE Confidence: 0.93397822

00:43:01.864 --> 00:43:03.208 because ferritin is also

NOTE Confidence: 0.93397822

00:43:03.208 --> 00:43:04.699 an acute phase reactant,

NOTE Confidence: 0.93397822

00:43:04.700 --> 00:43:06.356 so it's also induced by inflammation,

NOTE Confidence: 0.93397822

00:43:06.360 --> 00:43:08.264 and if you have liver disease or malignancy,

NOTE Confidence: 0.93397822

00:43:08.270 --> 00:43:09.596 these things kind of affect ferritin,

NOTE Confidence: 0.93397822

00:43:09.600 --> 00:43:12.100 so it makes it very hard if ferritin is low,

NOTE Confidence: 0.93397822

00:43:12.100 --> 00:43:13.591 it's a good indicator that iron stores

NOTE Confidence: 0.93397822

00:43:13.591 --> 00:43:15.400 are low, but if ferritin is not low,

NOTE Confidence: 0.93397822

00:43:15.400 --> 00:43:17.276 it's hard to know is it's from

NOTE Confidence: 0.93397822

00:43:17.276 --> 00:43:18.660 inflammation is it's from iron,

NOTE Confidence: 0.93397822

00:43:18.660 --> 00:43:22.346 so we do need better tests and and

NOTE Confidence: 0.93397822

00:43:22.346 --> 00:43:23.874 you know transparent saturation.

NOTE Confidence: 0.93397822

00:43:23.880 --> 00:43:25.028 You know it's helpful,

NOTE Confidence: 0.93397822

00:43:25.028 --> 00:43:26.463 but I think functional markers

NOTE Confidence: 0.93397822

00:43:26.463 --> 00:43:27.289 would be useful.

NOTE Confidence: 0.93397822

00:43:27.290 --> 00:43:29.887 I think there's some interest in in

NOTE Confidence: 0.93397822

00:43:29.887 --> 00:43:32.519 trying to adapt more widely things

NOTE Confidence: 0.93397822

00:43:32.519 --> 00:43:34.919 like reticulocyte hemoglobin or a

NOTE Confidence: 0.93397822

00:43:34.919 --> 00:43:37.490 percentage of hypochromic red cells

NOTE Confidence: 0.93397822

00:43:37.490 --> 00:43:40.040 which are more functional markers.

NOTE Confidence: 0.93397822

00:43:40.040 --> 00:43:42.686 But I think we this is 1 area where

NOTE Confidence: 0.93397822

00:43:42.686 --> 00:43:45.572 we need more work to develop better

NOTE Confidence: 0.93397822

00:43:45.572 --> 00:43:48.224 biomarkers to help us understand what

NOTE Confidence: 0.93397822

00:43:48.224 --> 00:43:51.360 the iron status of our patients are.

NOTE Confidence: 0.93397822

00:43:51.360 --> 00:43:53.968 Karen I was curious about.

NOTE Confidence: 0.853120551130435

00:44:11.800 --> 00:44:13.000 Yeah, I think that's a good

NOTE Confidence: 0.853120551130435

00:44:13.000 --> 00:44:14.249 question and you know when Aiden

NOTE Confidence: 0.853120551130435

00:44:14.249 --> 00:44:15.269 was first discovered there was

NOTE Confidence: 0.853120551130435

00:44:15.269 --> 00:44:16.778 a lot of interest in thinking.

NOTE Confidence: 0.853120551130435

00:44:16.780 --> 00:44:18.082 Oh, can we use hepcidin as

NOTE Confidence: 0.853120551130435

00:44:18.082 --> 00:44:19.439 a new biomarker to you know?

NOTE Confidence: 0.853120551130435

00:44:19.440 --> 00:44:21.720 Figure out if patients are,

NOTE Confidence: 0.853120551130435

00:44:21.720 --> 00:44:22.960 you know, truly are deficient

NOTE Confidence: 0.853120551130435

00:44:22.960 --> 00:44:23.952 or functionally are deficient,

NOTE Confidence: 0.853120551130435

00:44:23.960 --> 00:44:25.728 but the problem is that have signed is

NOTE Confidence: 0.853120551130435

00:44:25.728 --> 00:44:27.247 regulated by so many different things

NOTE Confidence: 0.853120551130435

00:44:27.247 --> 00:44:28.783 that are changing in our patients.

NOTE Confidence: 0.853120551130435

00:44:28.790 --> 00:44:30.950 People have shown that erythropoietin

NOTE Confidence: 0.853120551130435

00:44:30.950 --> 00:44:32.678 suppresses subsided in in

NOTE Confidence: 0.853120551130435

00:44:32.678 --> 00:44:34.664 kidney disease patients in no.

NOTE Confidence: 0.853120551130435

00:44:34.664 --> 00:44:36.146 It's induced by inflammation if you

NOTE Confidence: 0.853120551130435

00:44:36.146 --> 00:44:37.818 give iron that will actually induce

NOTE Confidence: 0.853120551130435

00:44:37.818 --> 00:44:39.790 subsidence of patients were an IV iron,

NOTE Confidence: 0.853120551130435

00:44:39.790 --> 00:44:40.166 you know,

NOTE Confidence: 0.853120551130435

00:44:40.166 --> 00:44:41.482 so it's there's so many factors that

NOTE Confidence: 0.853120551130435

00:44:41.482 --> 00:44:43.027 are influencing have signed expression.

NOTE Confidence: 0.853120551130435

00:44:43.030 --> 00:44:45.076 I think that's why it hasn't

NOTE Confidence: 0.853120551130435

00:44:45.076 --> 00:44:47.249 necessarily been useful as a biomarker.

NOTE Confidence: 0.853120551130435

00:44:47.250 --> 00:44:48.966 You know the group that discovered

NOTE Confidence: 0.853120551130435

00:44:48.966 --> 00:44:50.110 everything Farren has developed

NOTE Confidence: 0.853120551130435

00:44:50.153 --> 00:44:51.593 and Eliza assay to measure Earth

NOTE Confidence: 0.853120551130435

00:44:51.593 --> 00:44:52.313 of Farrah levels.

NOTE Confidence: 0.853120551130435

00:44:52.320 --> 00:44:54.098 And I know this is something that

NOTE Confidence: 0.853120551130435

00:44:54.098 --> 00:44:55.748 they're that people are looking into as

NOTE Confidence: 0.853120551130435

00:44:55.748 --> 00:44:57.879 to whether that can be a useful biomarker.

NOTE Confidence: 0.893815143333333

00:45:13.340 --> 00:45:15.824 So the question is, what do we know about?

NOTE Confidence: 0.24480686

00:45:20.330 --> 00:45:20.830 Specifically.

NOTE Confidence: 0.867318836666667

00:45:23.980 --> 00:45:25.360 Yeah, so that's a great question.

NOTE Confidence: 0.867318836666667

00:45:25.360 --> 00:45:26.435 I think it's not just

NOTE Confidence: 0.867318836666667

00:45:26.435 --> 00:45:27.295 macrophages in the spleen,

NOTE Confidence: 0.867318836666667

00:45:27.300 --> 00:45:28.938 I think that's classically thought about,

NOTE Confidence: 0.867318836666667

00:45:28.940 --> 00:45:31.094 but actually there there was a

NOTE Confidence: 0.867318836666667

00:45:31.094 --> 00:45:33.900 study that I was part of where

NOTE Confidence: 0.867318836666667

00:45:33.900 --> 00:45:36.050 they actually did certain like.

NOTE Confidence: 0.867318836666667

00:45:36.050 --> 00:45:37.802 Partial hepatectomy and compared it with

NOTE Confidence: 0.867318836666667

00:45:37.802 --> 00:45:39.896 splenectomy to look at how his iron where

NOTE Confidence: 0.867318836666667

00:45:39.896 --> 00:45:41.720 is most of the iron turnover happening.

NOTE Confidence: 0.867318836666667

00:45:41.720 --> 00:45:43.729 And it turns out that that the

NOTE Confidence: 0.867318836666667

00:45:43.729 --> 00:45:45.247 liver macrophages also play an

NOTE Confidence: 0.867318836666667

00:45:45.247 --> 00:45:47.035 important role in an iron recycling.

NOTE Confidence: 0.867318836666667

00:45:47.040 --> 00:45:49.460 It's not just swing.

NOTE Confidence: 0.867318836666667

00:45:49.460 --> 00:45:51.092 I don't think that much is

NOTE Confidence: 0.867318836666667

00:45:51.092 --> 00:45:52.180 known about kidney macrophages.

NOTE Confidence: 0.867318836666667

00:45:52.180 --> 00:45:54.076 As far as how much of a role

NOTE Confidence: 0.867318836666667

00:45:54.076 --> 00:45:55.738 they play in iron recycling,

NOTE Confidence: 0.867318836666667

00:45:55.740 --> 00:45:57.865 it's at the the spleen, and the liver

NOTE Confidence: 0.867318836666667

00:45:57.865 --> 00:45:59.140 are probably the predominant sites.

NOTE Confidence: 0.867318836666667

00:45:59.140 --> 00:46:00.292 But it's an interesting

NOTE Confidence: 0.867318836666667

00:46:00.292 --> 00:46:01.444 question and you know,

NOTE Confidence: 0.867318836666667

00:46:01.450 --> 00:46:03.238 there's there these sort of conflicting

NOTE Confidence: 0.867318836666667

00:46:03.238 --> 00:46:05.458 data about is iron helpful or harmful,

NOTE Confidence: 0.867318836666667

00:46:05.460 --> 00:46:06.496 and acute kidney injury.

NOTE Confidence: 0.867318836666667

00:46:06.496 --> 00:46:08.050 And I think part of it

NOTE Confidence: 0.867318836666667

00:46:08.110 --> 00:46:09.490 may be where the iron is.

NOTE Confidence: 0.867318836666667

00:46:09.490 --> 00:46:10.495 There's you know.

NOTE Confidence: 0.867318836666667

00:46:10.495 --> 00:46:11.500 Macrophages are designed

NOTE Confidence: 0.867318836666667

00:46:11.500 --> 00:46:12.840 to store iron safely,

NOTE Confidence: 0.867318836666667

00:46:12.840 --> 00:46:14.230 and there's some evidence that,

NOTE Confidence: 0.867318836666667

00:46:14.230 --> 00:46:15.328 like with preconditioning,

NOTE Confidence: 0.867318836666667

00:46:15.328 --> 00:46:16.792 you can induce protective

NOTE Confidence: 0.867318836666667

00:46:16.792 --> 00:46:17.524 antioxidant pathways.

NOTE Confidence: 0.867318836666667

00:46:17.530 --> 00:46:18.970 And maybe that's a good thing,

NOTE Confidence: 0.867318836666667

00:46:18.970 --> 00:46:21.250 but it probably depends where the iron is,

NOTE Confidence: 0.867318836666667

00:46:21.250 --> 00:46:22.384 and I think when you're thinking

NOTE Confidence: 0.867318836666667

00:46:22.384 --> 00:46:23.790 about iron levels of different organs,

NOTE Confidence: 0.867318836666667

00:46:23.790 --> 00:46:25.342 that's an important point.

NOTE Confidence: 0.867318836666667

00:46:25.342 --> 00:46:26.506 But that's not.

NOTE Confidence: 0.867318836666667

00:46:26.510 --> 00:46:28.085 I don't know that a lot of

NOTE Confidence: 0.867318836666667

00:46:28.085 --> 00:46:29.550 work has been done on that.

NOTE Confidence: 0.867318836666667

00:46:29.550 --> 00:46:31.150 I think that's an interesting

NOTE Confidence: 0.867318836666667

00:46:31.150 --> 00:46:32.430 area for future research.

NOTE Confidence: 0.462609646666667

00:46:44.860 --> 00:46:45.868 Not that progress.

NOTE Confidence: 0.885585891

00:47:03.880 --> 00:47:06.110 The next speaker is Doctor

NOTE Confidence: 0.885585891

00:47:06.110 --> 00:47:08.340 Peter Harris from Mayo Clinic,

NOTE Confidence: 0.885585891

00:47:08.340 --> 00:47:11.280 and he'll be discussing genetic

NOTE Confidence: 0.885585891

00:47:11.280 --> 00:47:13.920 complexity in AD PKD. Well.

NOTE Confidence: 0.836409810230769

00:47:18.250 --> 00:47:21.730 So I went to thank Judy and the

NOTE Confidence: 0.836409810230769

00:47:21.730 --> 00:47:24.308 organizers for inviting me here.

NOTE Confidence: 0.836409810230769

00:47:24.310 --> 00:47:26.277 I mean it's we will appreciate the

NOTE Confidence: 0.836409810230769

00:47:26.277 --> 00:47:28.423 work that the O'Brien Center is on

NOTE Confidence: 0.836409810230769

00:47:28.423 --> 00:47:30.283 the P80 Centers for that matter,

NOTE Confidence: 0.836409810230769

00:47:30.290 --> 00:47:33.210 do around the country providing

NOTE Confidence: 0.836409810230769

00:47:33.210 --> 00:47:36.130 resources for for kidney research.

NOTE Confidence: 0.836409810230769

00:47:36.130 --> 00:47:37.640 So I'm doing something a

NOTE Confidence: 0.836409810230769

00:47:37.640 --> 00:47:38.546 little dangerous here.

NOTE Confidence: 0.836409810230769

00:47:38.550 --> 00:47:40.646 I'm talking about a PKD at Yale and

NOTE Confidence: 0.836409810230769

00:47:40.646 --> 00:47:42.738 think that some people here may know

NOTE Confidence: 0.836409810230769

00:47:42.738 --> 00:47:44.589 more about the disease than I do,

NOTE Confidence: 0.836409810230769

00:47:44.590 --> 00:47:47.174 but I'll try and stick to the genetic.

NOTE Confidence: 0.836409810230769

00:47:47.180 --> 00:47:50.141 Aspects of the disease and and and

NOTE Confidence: 0.836409810230769

00:47:50.141 --> 00:47:53.181 see what our understanding of the

NOTE Confidence: 0.836409810230769

00:47:53.181 --> 00:47:56.529 complexity of this disease can provide

NOTE Confidence: 0.836409810230769

00:47:56.529 --> 00:48:00.429 in terms of understanding pathogenesis.

NOTE Confidence: 0.836409810230769

00:48:00.430 --> 00:48:04.366 So you know about 80 PKD.

NOTE Confidence: 0.836409810230769

00:48:04.370 --> 00:48:07.286 This is a a common genetic

NOTE Confidence: 0.836409810230769

00:48:07.286 --> 00:48:09.850 disease about one in 1000.

NOTE Confidence: 0.836409810230769

00:48:09.850 --> 00:48:11.610 Individuals have this disorder.

NOTE Confidence: 0.836409810230769

00:48:11.610 --> 00:48:14.250 It's a progressive disease that develops

NOTE Confidence: 0.836409810230769

00:48:14.312 --> 00:48:16.388 over the lifetime of the patients,

NOTE Confidence: 0.836409810230769

00:48:16.390 --> 00:48:19.300 so that 50% of patients experienced

NOTE Confidence: 0.836409810230769

00:48:19.300 --> 00:48:21.683 renal failure around 60 years

NOTE Confidence: 0.836409810230769

00:48:21.683 --> 00:48:24.846 of age and about 5% of the the

NOTE Confidence: 0.836409810230769

00:48:24.846 --> 00:48:27.420 population that has on dialysis or

NOTE Confidence: 0.836409810230769

00:48:27.510 --> 00:48:30.370 transplantation in this country.

NOTE Confidence: 0.836409810230769

00:48:30.370 --> 00:48:33.135 Has ADPKD and and worldwide

NOTE Confidence: 0.836409810230769

00:48:33.135 --> 00:48:35.900 that number is even higher.

NOTE Confidence: 0.836409810230769

00:48:35.900 --> 00:48:40.535 So the the major genes are peak 81 and

NOTE Confidence: 0.836409810230769

00:48:40.540 --> 00:48:43.316 P82P-81 is a a kind of complicated gene,

NOTE Confidence: 0.836409810230769

00:48:43.320 --> 00:48:46.057 has an open reading frame or a

NOTE Confidence: 0.836409810230769

00:48:46.057 --> 00:48:48.400 coding region of nearly 13 KB.

NOTE Confidence: 0.836409810230769

00:48:48.400 --> 00:48:51.436 It lies on the light green.

NOTE Confidence: 0.836409810230769

00:48:51.440 --> 00:48:54.079 Here shows that the area that lies

NOTE Confidence: 0.836409810230769

00:48:54.079 --> 00:48:56.607 within a duplicated part of the genome.

NOTE Confidence: 0.836409810230769

00:48:56.610 --> 00:48:59.364 So even though now with whole

NOTE Confidence: 0.836409810230769

00:48:59.364 --> 00:49:01.200 exome sequencing and capturing

NOTE Confidence: 0.836409810230769

00:49:01.277 --> 00:49:03.755 methods it's still a little tricky

NOTE Confidence: 0.836409810230769

00:49:03.755 --> 00:49:05.790 to screen this gene for.

NOTE Confidence: 0.836409810230769

00:49:05.790 --> 00:49:07.226 Pathogenic variants.

NOTE Confidence: 0.836409810230769

00:49:07.226 --> 00:49:12.252 Peak 82 is a more normal gene.

NOTE Confidence: 0.836409810230769

00:49:12.260 --> 00:49:14.846 An open reading frame of about

NOTE Confidence: 0.836409810230769

00:49:14.846 --> 00:49:17.730 3 KB here with a 15 exons,

NOTE Confidence: 0.836409810230769

00:49:17.730 --> 00:49:21.307 so about 78% of patients have PKD,

NOTE Confidence: 0.836409810230769

00:49:21.310 --> 00:49:24.306 one as the cause of their ADP

NOTE Confidence: 0.836409810230769

00:49:24.306 --> 00:49:28.171 KD and about 15% PKD 2 and

NOTE Confidence: 0.836409810230769

00:49:28.171 --> 00:49:31.433 then we for the remaining 7%.

NOTE Confidence: 0.836409810230769

00:49:31.433 --> 00:49:34.048 Some of these are unresolved,

NOTE Confidence: 0.836409810230769

00:49:34.050 --> 00:49:35.314 there's some other loci.

NOTE Confidence: 0.836409810230769

00:49:35.314 --> 00:49:38.343 That I'm going to go on to talk about

NOTE Confidence: 0.836409810230769

00:49:38.343 --> 00:49:40.118 and some other genetic complexity

NOTE Confidence: 0.836409810230769

00:49:40.118 --> 00:49:42.218 that I want to mention too.

NOTE Confidence: 0.428407731666667

00:49:44.640 --> 00:49:47.280 So a PKD or PKD 1?

NOTE Confidence: 0.428407731666667

00:49:47.280 --> 00:49:49.722 PKD 2 are very likely heterogeneous

NOTE Confidence: 0.428407731666667

00:49:49.722 --> 00:49:52.477 as a wide range of different

NOTE Confidence: 0.428407731666667

00:49:52.477 --> 00:49:55.097 mutations that cause the disease.

NOTE Confidence: 0.428407731666667

00:49:55.100 --> 00:49:57.260 If we look at the different

NOTE Confidence: 0.428407731666667

00:49:57.260 --> 00:49:59.576 types of mutations that we can

NOTE Confidence: 0.428407731666667

00:49:59.576 --> 00:50:01.176 find causing human disease,

NOTE Confidence: 0.428407731666667

00:50:01.180 --> 00:50:03.190 then all of those are represented

NOTE Confidence: 0.428407731666667

00:50:03.190 --> 00:50:05.642 here for beginning one we can see the

NOTE Confidence: 0.428407731666667

00:50:05.642 --> 00:50:07.820 mutations are in all parts of the gene.

NOTE Confidence: 0.428407731666667

00:50:07.820 --> 00:50:09.300 There's no real hot spots,

NOTE Confidence: 0.428407731666667

00:50:09.300 --> 00:50:12.375 although some areas probably have

NOTE Confidence: 0.428407731666667

00:50:12.375 --> 00:50:15.450 an enrichment for missense changes.

NOTE Confidence: 0.428407731666667

00:50:15.450 --> 00:50:18.434 I think 80 PKD is a common disease

NOTE Confidence: 0.428407731666667

00:50:18.434 --> 00:50:21.219 because any single inactivating variant

NOTE Confidence: 0.428407731666667

00:50:21.219 --> 00:50:24.469 can cause polycystic kidney disease.

NOTE Confidence: 0.428407731666667

00:50:24.470 --> 00:50:26.468 There's no single variant accounts for

NOTE Confidence: 0.428407731666667

00:50:26.468 --> 00:50:29.570 more than 2% of the families worldwide,

NOTE Confidence: 0.428407731666667

00:50:29.570 --> 00:50:32.198 and there's over 1600 different

NOTE Confidence: 0.428407731666667

00:50:32.198 --> 00:50:34.818 variants that have been described.

NOTE Confidence: 0.844536944

00:50:38.100 --> 00:50:40.140 So as well as genetics,

NOTE Confidence: 0.844536944

00:50:40.140 --> 00:50:43.254 we can use the size of the kidneys to

NOTE Confidence: 0.844536944

00:50:43.254 --> 00:50:45.737 determine the severity of the disease.

NOTE Confidence: 0.844536944

00:50:45.740 --> 00:50:48.548 This is work done by Maria Rosabel at

NOTE Confidence: 0.844536944

00:50:48.548 --> 00:50:51.261 Mayo and the idea here is to divide

NOTE Confidence: 0.844536944

00:50:51.261 --> 00:50:54.061 the the size of the kidney divided by

NOTE Confidence: 0.844536944

00:50:54.061 --> 00:50:58.510 the hate at the height of the patient.

NOTE Confidence: 0.844536944

00:50:58.510 --> 00:51:01.195 So total kidney volume measured

NOTE Confidence: 0.844536944

00:51:01.195 --> 00:51:04.280 by MRI and then determining put

NOTE Confidence: 0.844536944

00:51:04.280 --> 00:51:06.280 them into different groups here.

NOTE Confidence: 0.844536944

00:51:06.280 --> 00:51:09.143 So these are obviously patients with larger

NOTE Confidence: 0.844536944

00:51:09.143 --> 00:51:11.778 kidneys and patients with smaller kidneys.

NOTE Confidence: 0.844536944

00:51:11.780 --> 00:51:14.764 And then if you look at the outcome

NOTE Confidence: 0.844536944

00:51:14.764 --> 00:51:18.504 of those measurements in terms of

NOTE Confidence: 0.844536944

00:51:18.504 --> 00:51:22.272 decline in renal function or EGFR.

NOTE Confidence: 0.844536944

00:51:22.280 --> 00:51:25.295 We can see that the larger kidneys are much

NOTE Confidence: 0.844536944

00:51:25.295 --> 00:51:27.922 more likely to proceed to more rapidly

NOTE Confidence: 0.844536944

00:51:27.922 --> 00:51:30.589 to renal failure on the on the list,

NOTE Confidence: 0.844536944

00:51:30.590 --> 00:51:32.876 smaller kidneys are less likely to.

NOTE Confidence: 0.782317843333333

00:51:34.930 --> 00:51:39.221 We did some analysis using both genotypic

NOTE Confidence: 0.782317843333333

00:51:39.221 --> 00:51:41.930 groups and a size to the kidneys,

NOTE Confidence: 0.782317843333333

00:51:41.930 --> 00:51:44.898 so the Mayo imaging class to look at

NOTE Confidence: 0.782317843333333

00:51:44.898 --> 00:51:47.777 outcomes in terms of end stage renal

NOTE Confidence: 0.782317843333333

00:51:47.777 --> 00:51:50.115 disease and we can see here that topic

NOTE Confidence: 0.782317843333333

00:51:50.115 --> 00:51:52.448 82 has been known for a long time,

NOTE Confidence: 0.782317843333333

00:51:52.450 --> 00:51:55.570 as the mildest form of the the disease,

NOTE Confidence: 0.782317843333333

00:51:55.570 --> 00:51:56.456 truncating peak.

NOTE Confidence: 0.782317843333333

00:51:56.456 --> 00:51:59.557 Anyone mutations have the and the average

NOTE Confidence: 0.782317843333333

00:51:59.557 --> 00:52:02.506 age and then stage of around 55 years,

NOTE Confidence: 0.782317843333333

00:52:02.510 --> 00:52:04.974 and then we divided the non truncating.

NOTE Confidence: 0.782317843333333

00:52:04.980 --> 00:52:05.796 Changes here,

NOTE Confidence: 0.782317843333333

00:52:05.796 --> 00:52:08.244 so these are mainly missense changes,

NOTE Confidence: 0.782317843333333

00:52:08.250 --> 00:52:10.070 but we've used bioinformatic methods

NOTE Confidence: 0.782317843333333

00:52:10.070 --> 00:52:12.919 to do to predict ones that are more

NOTE Confidence: 0.782317843333333

00:52:12.919 --> 00:52:14.839 likely to be fully penetrant and

NOTE Confidence: 0.782317843333333

00:52:14.839 --> 00:52:17.047 less likely to be fully penetrant.

NOTE Confidence: 0.782317843333333

00:52:17.050 --> 00:52:19.290 And you can see that these fit

NOTE Confidence: 0.782317843333333

00:52:19.290 --> 00:52:21.180 in somewhere between the the

NOTE Confidence: 0.782317843333333

00:52:21.180 --> 00:52:23.970 peak 81 truncating and peak 82.

NOTE Confidence: 0.782317843333333

00:52:23.970 --> 00:52:25.769 If we look at the imaging classes,

NOTE Confidence: 0.782317843333333

00:52:25.770 --> 00:52:28.338 you can see that the patients which would

NOTE Confidence: 0.782317843333333

00:52:28.338 --> 00:52:30.744 have the smallest kidneys don't usually

NOTE Confidence: 0.782317843333333

00:52:30.744 --> 00:52:33.288 proceed to end stage renal disease,

NOTE Confidence: 0.782317843333333

00:52:33.290 --> 00:52:35.600 whereas the ones with larger kidneys.

NOTE Confidence: 0.782317843333333

00:52:35.600 --> 00:52:37.574 Have an average age event stage at

NOTE Confidence: 0.782317843333333

00:52:37.574 --> 00:52:40.072 45 years so we can see that the the

NOTE Confidence: 0.782317843333333

00:52:40.072 --> 00:52:42.661 size of the kidneys is a is a fairly

NOTE Confidence: 0.782317843333333

00:52:42.661 --> 00:52:44.131 good predictor of when patients

NOTE Confidence: 0.782317843333333

00:52:44.140 --> 00:52:46.126 are going to reach end stage,

NOTE Confidence: 0.782317843333333

00:52:46.130 --> 00:52:48.056 although with all of these measurements

NOTE Confidence: 0.782317843333333

00:52:48.056 --> 00:52:50.718 as quite a a spread here in the

NOTE Confidence: 0.782317843333333

00:52:50.718 --> 00:52:51.699 in the population.

NOTE Confidence: 0.782317843333333

00:52:51.700 --> 00:52:54.528 So obviously the size of the kidney

NOTE Confidence: 0.782317843333333

00:52:54.528 --> 00:52:57.880 is is reflecting more than just the

NOTE Confidence: 0.782317843333333

00:52:57.880 --> 00:52:59.940 the germline mutation information.

NOTE Confidence: 0.782317843333333

00:52:59.940 --> 00:53:02.852 Probably other genetic modifiers

NOTE Confidence: 0.782317843333333

00:53:02.852 --> 00:53:06.492 and other phenotypic and lifestyle.

NOTE Confidence: 0.782317843333333

00:53:06.500 --> 00:53:08.810 And factors that are influencing

NOTE Confidence: 0.782317843333333

00:53:08.810 --> 00:53:11.120 the severity of the disease.

NOTE Confidence: 0.836697217307692

00:53:13.210 --> 00:53:16.388 We looked at how the disease progresses

NOTE Confidence: 0.836697217307692

00:53:16.388 --> 00:53:19.733 in terms of decline in the EGFR

NOTE Confidence: 0.836697217307692

00:53:19.733 --> 00:53:22.565 of both by these genotypic groups

NOTE Confidence: 0.836697217307692

00:53:22.658 --> 00:53:25.508 and by the imaging classes here,

NOTE Confidence: 0.836697217307692

00:53:25.510 --> 00:53:27.028 the kind of classical view in

NOTE Confidence: 0.836697217307692

00:53:27.028 --> 00:53:28.848 80P KD is kind of like this.

NOTE Confidence: 0.836697217307692

00:53:28.850 --> 00:53:30.900 I think, where patients have

NOTE Confidence: 0.836697217307692

00:53:30.900 --> 00:53:32.950 preserved renal function for a

NOTE Confidence: 0.836697217307692

00:53:33.025 --> 00:53:35.524 while and then it starts to decline.

NOTE Confidence: 0.836697217307692

00:53:35.530 --> 00:53:37.343 But we found, at least in the

NOTE Confidence: 0.836697217307692

00:53:37.343 --> 00:53:38.590 the most severe groups,

NOTE Confidence: 0.836697217307692

00:53:38.590 --> 00:53:40.726 the patients with the largest kidneys

NOTE Confidence: 0.836697217307692

00:53:40.726 --> 00:53:43.190 and also pick any one truncating.

NOTE Confidence: 0.836697217307692

00:53:43.190 --> 00:53:46.102 Mutations was a decline from a fairly

NOTE Confidence: 0.836697217307692

00:53:46.102 --> 00:53:49.320 early age and in a fairly linear way.

NOTE Confidence: 0.836697217307692

00:53:49.320 --> 00:53:51.552 For these more severe groups and

NOTE Confidence: 0.836697217307692

00:53:51.552 --> 00:53:53.757 only in the milder groups did

NOTE Confidence: 0.836697217307692

00:53:53.757 --> 00:53:55.944 we see this preservation of of

NOTE Confidence: 0.836697217307692

00:53:55.944 --> 00:53:58.392 function and then decline later on.

NOTE Confidence: 0.836697217307692

00:53:58.400 --> 00:53:59.470 And as you see here,

NOTE Confidence: 0.836697217307692

00:53:59.470 --> 00:54:01.906 the 1A not really a declining

NOTE Confidence: 0.836697217307692

00:54:01.906 --> 00:54:03.530 into to renal failure.

NOTE Confidence: 0.872888561666667

00:54:06.350 --> 00:54:09.913 We also looked at how the kidneys

NOTE Confidence: 0.872888561666667

00:54:09.913 --> 00:54:12.570 increase in size over time,

NOTE Confidence: 0.872888561666667

00:54:12.570 --> 00:54:16.385 depending again on these same groups and

NOTE Confidence: 0.872888561666667

00:54:16.385 --> 00:54:19.705 and for P-80 for the different P-81 groups.

NOTE Confidence: 0.872888561666667

00:54:19.710 --> 00:54:21.924 It was not really a significant

NOTE Confidence: 0.872888561666667

00:54:21.924 --> 00:54:24.489 difference in the way that the that

NOTE Confidence: 0.872888561666667

00:54:24.489 --> 00:54:27.243 the the speed of the progression

NOTE Confidence: 0.872888561666667

00:54:27.243 --> 00:54:30.544 of the disease for for the imaging

NOTE Confidence: 0.872888561666667

00:54:30.544 --> 00:54:33.298 class we can see some difference

NOTE Confidence: 0.872888561666667

00:54:33.387 --> 00:54:36.299 here with a with a lower rate of.

NOTE Confidence: 0.872888561666667

00:54:36.300 --> 00:54:39.681 Of progression here for 1A and 1B

NOTE Confidence: 0.872888561666667

00:54:39.681 --> 00:54:43.064 compared to the 1E and 1D groups.

NOTE Confidence: 0.872888561666667

00:54:43.064 --> 00:54:46.160 If we look at them together on the

NOTE Confidence: 0.872888561666667

00:54:46.252 --> 00:54:49.180 on the same slide we can see here,

NOTE Confidence: 0.872888561666667

00:54:49.180 --> 00:54:52.274 but I've showed you with this kind

NOTE Confidence: 0.872888561666667

00:54:52.274 --> 00:54:55.460 of rapid decline in renal function in

NOTE Confidence: 0.872888561666667

00:54:55.460 --> 00:54:59.315 terms of EGFR for the for the larger

NOTE Confidence: 0.872888561666667

00:54:59.315 --> 00:55:02.724 kidneys and then preserved for the for

NOTE Confidence: 0.872888561666667

00:55:02.824 --> 00:55:06.316 the for the for the for the smaller kidneys.

NOTE Confidence: 0.872888561666667

00:55:06.320 --> 00:55:08.255 If we look at the the genotype here we

NOTE Confidence: 0.872888561666667

00:55:08.255 --> 00:55:10.366 can see there's not really a difference,

NOTE Confidence: 0.872888561666667

00:55:10.370 --> 00:55:12.278 although there is a difference in

NOTE Confidence: 0.872888561666667

00:55:12.278 --> 00:55:14.758 the in the start of the recordings.

NOTE Confidence: 0.872888561666667

00:55:14.760 --> 00:55:17.091 Even at 20 years of age and we can

NOTE Confidence: 0.872888561666667

00:55:17.091 --> 00:55:19.432 see that that's even clearer here

NOTE Confidence: 0.872888561666667

00:55:19.432 --> 00:55:21.040 in the imaging classes,

NOTE Confidence: 0.872888561666667

00:55:21.040 --> 00:55:23.518 so that's just telling us before 20

NOTE Confidence: 0.872888561666667

00:55:23.518 --> 00:55:25.851 years of age during the pediatric

NOTE Confidence: 0.872888561666667

00:55:25.851 --> 00:55:29.071 period that the the the rate that the

NOTE Confidence: 0.872888561666667

00:55:29.071 --> 00:55:31.549 kidneys grow is quite a lot different

NOTE Confidence: 0.872888561666667

00:55:31.549 --> 00:55:34.114 in the patients which are going to have

NOTE Confidence: 0.872888561666667

00:55:34.114 --> 00:55:36.518 the worst outcomes with the largest kidneys.

NOTE Confidence: 0.872888561666667

00:55:36.520 --> 00:55:38.850 Compared to the largest cities

NOTE Confidence: 0.872888561666667

00:55:38.850 --> 00:55:41.180 compared to the smaller kidneys

NOTE Confidence: 0.872888561666667

00:55:41.262 --> 00:55:43.518 and also for PKD 1 truncation,

NOTE Confidence: 0.872888561666667

00:55:43.520 --> 00:55:45.424 they also develop more

NOTE Confidence: 0.872888561666667

00:55:45.424 --> 00:55:47.328 quickly during that period.

NOTE Confidence: 0.872888561666667

00:55:47.330 --> 00:55:49.814 So it seems like the development

NOTE Confidence: 0.872888561666667

00:55:49.814 --> 00:55:52.389 and growth of kidneys during this

NOTE Confidence: 0.872888561666667

00:55:52.390 --> 00:55:55.480 pediatric period is important for

NOTE Confidence: 0.872888561666667

00:55:55.480 --> 00:55:59.050 determining the the outcomes of the.

NOTE Confidence: 0.872888561666667

00:55:59.050 --> 00:56:00.190 The patients.

NOTE Confidence: 0.89702069

00:56:02.290 --> 00:56:04.168 So this would be the bottom.

NOTE Confidence: 0.89702069

00:56:04.170 --> 00:56:07.166 Here would be our typical 80 P80

NOTE Confidence: 0.89702069

00:56:07.166 --> 00:56:09.587 pedigree where it's inherited in a

NOTE Confidence: 0.89702069

00:56:09.587 --> 00:56:11.861 dominant fashion of males and females

NOTE Confidence: 0.89702069

00:56:11.861 --> 00:56:14.070 are affected but but we don't.

NOTE Confidence: 0.89702069

00:56:14.070 --> 00:56:16.667 We quite often see this setup where

NOTE Confidence: 0.89702069

00:56:16.667 --> 00:56:19.233 apparently we have a a new mutation

NOTE Confidence: 0.89702069

00:56:19.233 --> 00:56:21.774 occurring in the in an individual here

NOTE Confidence: 0.89702069

00:56:21.774 --> 00:56:24.210 with sibs and the parents apparently

NOTE Confidence: 0.89702069

00:56:24.210 --> 00:56:27.524 unaffected and at least 10 to 20% of 80

NOTE Confidence: 0.89702069

00:56:27.524 --> 00:56:30.357 P80 families have this type of structure

NOTE Confidence: 0.89702069

00:56:30.357 --> 00:56:33.057 where we suspect that the Dinovo.

NOTE Confidence: 0.89702069

00:56:33.060 --> 00:56:35.760 Mutation has occurred.

NOTE Confidence: 0.89702069

00:56:35.760 --> 00:56:37.475 One possibility with the DENOVO

NOTE Confidence: 0.89702069

00:56:37.475 --> 00:56:39.532 mutation is that it hasn't occurred

NOTE Confidence: 0.89702069

00:56:39.532 --> 00:56:41.499 in the sperm or the egg here,

NOTE Confidence: 0.89702069

00:56:41.500 --> 00:56:43.714 but it's occurred at a later

NOTE Confidence: 0.89702069

00:56:43.714 --> 00:56:46.139 stage of four cell stage here,

NOTE Confidence: 0.89702069

00:56:46.140 --> 00:56:49.492 and the result of that is that the

NOTE Confidence: 0.89702069

00:56:49.492 --> 00:56:53.057 patient is a mosaic of of cells that

NOTE Confidence: 0.89702069

00:56:53.057 --> 00:56:56.302 have the the mutation of ones that

NOTE Confidence: 0.89702069

00:56:56.302 --> 00:56:59.098 don't have the the the mutation.

NOTE Confidence: 0.89702069

00:56:59.100 --> 00:57:01.332 Then this has an influence on

NOTE Confidence: 0.89702069

00:57:01.332 --> 00:57:02.820 how the disease progresses,

NOTE Confidence: 0.89702069

00:57:02.820 --> 00:57:04.161 presents and progresses.

NOTE Confidence: 0.89702069

00:57:04.161 --> 00:57:05.949 If we look at.

NOTE Confidence: 0.89702069

00:57:05.950 --> 00:57:07.415 That we published a paper

NOTE Confidence: 0.89702069

00:57:07.415 --> 00:57:08.880 a couple of years ago,

NOTE Confidence: 0.89702069

00:57:08.880 --> 00:57:10.722 about 20 families that with mosaicism

NOTE Confidence: 0.89702069

00:57:10.722 --> 00:57:13.366 and this is an example of one of them.

NOTE Confidence: 0.89702069

00:57:13.370 --> 00:57:15.890 Here, the mother is a mosaic.

NOTE Confidence: 0.89702069

00:57:15.890 --> 00:57:18.146 Can see this rather odd pattern

NOTE Confidence: 0.89702069

00:57:18.146 --> 00:57:20.270 of a rather small number,

NOTE Confidence: 0.89702069

00:57:20.270 --> 00:57:22.454 but at large assess within the

NOTE Confidence: 0.89702069

00:57:22.454 --> 00:57:25.210 kidney you can see the sun here

NOTE Confidence: 0.89702069

00:57:25.210 --> 00:57:26.842 has more typical presentation

NOTE Confidence: 0.89702069

00:57:26.842 --> 00:57:29.708 and now this is at 20 years of

NOTE Confidence: 0.89702069

00:57:29.708 --> 00:57:31.956 age compared to 47 years of age

NOTE Confidence: 0.89702069

00:57:31.956 --> 00:57:34.014 when we did the genetic analysis

NOTE Confidence: 0.89702069

00:57:34.014 --> 00:57:36.358 we're able to find this insertion.

NOTE Confidence: 0.89702069

00:57:36.360 --> 00:57:37.536 Deletion mutation.

NOTE Confidence: 0.89702069

00:57:37.536 --> 00:57:40.860 That's a 50% of the cells in the sun,

NOTE Confidence: 0.89702069

00:57:40.860 --> 00:57:43.604 but only at 17% of cells in the

NOTE Confidence: 0.89702069

00:57:43.604 --> 00:57:46.099 in the in the mother here,

NOTE Confidence: 0.89702069

00:57:46.100 --> 00:57:49.518 so we can see that this lower

NOTE Confidence: 0.89702069

00:57:49.518 --> 00:57:52.031 level of of mutant cells leads to

NOTE Confidence: 0.89702069

00:57:52.031 --> 00:57:54.977 a a milder progression of disease,

NOTE Confidence: 0.89702069

00:57:54.980 --> 00:57:56.740 and if we look at the data overall,

NOTE Confidence: 0.89702069

00:57:56.740 --> 00:57:58.480 we can see that here.

NOTE Confidence: 0.89702069

00:57:58.480 --> 00:58:00.136 I hope you can see the red spots.

NOTE Confidence: 0.89702069

00:58:00.140 --> 00:58:02.612 Here are the mosaics and the other is

NOTE Confidence: 0.89702069

00:58:02.612 --> 00:58:04.883 a control population of similar types

NOTE Confidence: 0.89702069

00:58:04.883 --> 00:58:06.888 of mutations and you can see that.

NOTE Confidence: 0.89702069

00:58:06.890 --> 00:58:09.225 They tend to have preserved

NOTE Confidence: 0.89702069

00:58:09.225 --> 00:58:12.093 kidney function and they have a

NOTE Confidence: 0.89702069

00:58:12.093 --> 00:58:14.793 smaller kidneys than we would see

NOTE Confidence: 0.89702069

00:58:14.793 --> 00:58:17.379 without the without the mosaicism.

NOTE Confidence: 0.89702069

00:58:17.380 --> 00:58:19.290 We're probably at least 1%

NOTE Confidence: 0.89702069

00:58:19.290 --> 00:58:21.018 of families with ADP.

NOTE Confidence: 0.89702069

00:58:21.018 --> 00:58:23.610 KD have this type of mosaicism,

NOTE Confidence: 0.89702069

00:58:23.610 --> 00:58:25.848 but maybe more than that because

NOTE Confidence: 0.89702069

00:58:25.848 --> 00:58:28.386 low level of mosaicism may not get

NOTE Confidence: 0.89702069

00:58:28.386 --> 00:58:30.661 into the blood cells that we usually

NOTE Confidence: 0.89702069

00:58:30.736 --> 00:58:32.840 screen for pathogenic variants.

NOTE Confidence: 0.828977714444444

00:58:36.010 --> 00:58:40.303 So as you know, by the by the name,

NOTE Confidence: 0.828977714444444

00:58:40.310 --> 00:58:42.370 a PKD is normally a

NOTE Confidence: 0.828977714444444

00:58:42.370 --> 00:58:43.606 dominantly inherited disease,

NOTE Confidence: 0.828977714444444

00:58:43.610 --> 00:58:47.234 but sometimes it's a biallelic or

NOTE Confidence: 0.828977714444444

00:58:47.234 --> 00:58:50.550 has a recessive inheritance pattern,

NOTE Confidence: 0.828977714444444

00:58:50.550 --> 00:58:52.972 and then you can see an example

NOTE Confidence: 0.828977714444444

00:58:52.972 --> 00:58:55.820 here in this consanguineous family.

NOTE Confidence: 0.828977714444444

00:58:55.820 --> 00:58:57.945 The only individuals that reached

NOTE Confidence: 0.828977714444444

00:58:57.945 --> 00:59:00.884 end stage here were ones that were

NOTE Confidence: 0.828977714444444

00:59:00.884 --> 00:59:02.964 homozygous for a missense change.

NOTE Confidence: 0.828977714444444

00:59:02.970 --> 00:59:04.548 You can see the missense change.

NOTE Confidence: 0.828977714444444

00:59:04.550 --> 00:59:07.412 Is it a well conceived position

NOTE Confidence: 0.828977714444444

00:59:07.412 --> 00:59:09.320 in Orthodox and homologs,

NOTE Confidence: 0.828977714444444

00:59:09.320 --> 00:59:11.553 and we can see that individuals that

NOTE Confidence: 0.828977714444444

00:59:11.553 --> 00:59:13.992 just had one copy of this variant

NOTE Confidence: 0.828977714444444

00:59:13.992 --> 00:59:16.104 tended to have very mild disease,

NOTE Confidence: 0.828977714444444

00:59:16.110 --> 00:59:19.632 like just a few cysts within

NOTE Confidence: 0.828977714444444

00:59:19.632 --> 00:59:21.980 the within the kidney.

NOTE Confidence: 0.828977714444444

00:59:21.980 --> 00:59:24.635 So it was a lot of controversy about this.

NOTE Confidence: 0.828977714444444

00:59:24.640 --> 00:59:26.180 People didn't really believe it,

NOTE Confidence: 0.828977714444444

00:59:26.180 --> 00:59:27.130 I guess.

NOTE Confidence: 0.828977714444444

00:59:27.130 --> 00:59:30.455 So we we developed a model which

NOTE Confidence: 0.828977714444444

00:59:30.455 --> 00:59:33.072 in mimic this RC,

NOTE Confidence: 0.828977714444444

00:59:33.072 --> 00:59:41.476 Leo and and this this showed that we have a.

NOTE Confidence: 0.828977714444444

00:59:41.480 --> 00:59:44.435 We have this inherited slowly

NOTE Confidence: 0.828977714444444

00:59:44.435 --> 00:59:48.502 inheritance of the the disease in the

NOTE Confidence: 0.828977714444444

00:59:48.502 --> 00:59:52.030 homozygous RC animals here so that the.

NOTE Confidence: 0.828977714444444

00:59:52.030 --> 00:59:54.125 A disease developed slowly over

NOTE Confidence: 0.828977714444444

00:59:54.125 --> 00:59:56.931 the the the lifetime of the the

NOTE Confidence: 0.828977714444444

00:59:56.931 --> 00:59:59.122 mouse up to 12 months of age.

NOTE Confidence: 0.828977714444444

00:59:59.130 --> 01:00:01.426 So this showing if we if we

NOTE Confidence: 0.828977714444444

01:00:01.426 --> 01:00:03.170 had two inactivating mutations,

NOTE Confidence: 0.828977714444444

01:00:03.170 --> 01:00:06.350 then the animal would die embryonically.

NOTE Confidence: 0.828977714444444

01:00:06.350 --> 01:00:08.894 And obviously if this was a

NOTE Confidence: 0.828977714444444

01:00:08.894 --> 01:00:10.590 variant of unknown significance,

NOTE Confidence: 0.828977714444444

01:00:10.590 --> 01:00:12.750 we wouldn't develop polycystic kidneys.

NOTE Confidence: 0.828977714444444

01:00:12.750 --> 01:00:15.318 So I think this is fairly good evidence

NOTE Confidence: 0.828977714444444

01:00:15.318 --> 01:00:17.738 that this is a a hypomorphic allele.

NOTE Confidence: 0.931042349230769

01:00:19.950 --> 01:00:21.000 I don't know how to get rid

NOTE Confidence: 0.931042349230769

01:00:21.000 --> 01:00:21.889 of this thing at the top.

NOTE Confidence: 0.931042349230769

01:00:21.890 --> 01:00:25.934 Any good ideas? Anyway,

NOTE Confidence: 0.931042349230769

01:00:25.934 --> 01:00:31.082 the so one other presentation of

NOTE Confidence: 0.931042349230769

01:00:31.082 --> 01:00:34.204 the disease that is unusual in ADP.

NOTE Confidence: 0.931042349230769

01:00:34.210 --> 01:00:37.578 KD is when we have very early onset

NOTE Confidence: 0.931042349230769

01:00:37.578 --> 01:00:40.011 disease where where it's represents

NOTE Confidence: 0.931042349230769

109

01:00:40.011 --> 01:00:43.005 very much like the recessive form

NOTE Confidence: 0.931042349230769

01:00:43.005 --> 01:00:45.830 of polycystic kidney disease.

NOTE Confidence: 0.931042349230769

01:00:45.830 --> 01:00:47.730 With this very large kidneys,

NOTE Confidence: 0.931042349230769

01:00:47.730 --> 01:00:50.889 even found in utero and this is a family

NOTE Confidence: 0.931042349230769

01:00:50.889 --> 01:00:53.670 with this very early onset disease.

NOTE Confidence: 0.931042349230769

01:00:53.670 --> 01:00:55.926 They had a a typical truncating.

NOTE Confidence: 0.931042349230769

01:00:55.930 --> 01:00:58.410 Mutation in the three individuals

NOTE Confidence: 0.931042349230769

01:00:58.410 --> 01:01:01.416 here that had a typical presentation

NOTE Confidence: 0.931042349230769

01:01:01.416 --> 01:01:04.896 of 80 PKD but in the child here,

NOTE Confidence: 0.931042349230769

01:01:04.900 --> 01:01:07.138 with the in utero onset disease,

NOTE Confidence: 0.931042349230769

01:01:07.140 --> 01:01:09.366 we found that the same hypomorphic

NOTE Confidence: 0.931042349230769

01:01:09.366 --> 01:01:12.356 variant that we found in the in the

NOTE Confidence: 0.931042349230769

01:01:12.356 --> 01:01:14.146 previous family in homozygosity was

NOTE Confidence: 0.931042349230769

01:01:14.146 --> 01:01:16.696 also inherited from the other allele.

NOTE Confidence: 0.931042349230769

01:01:16.700 --> 01:01:19.591 So we think together these are lowering

NOTE Confidence: 0.931042349230769

01:01:19.591 --> 01:01:22.886 the level of the the POLICYSTAT expression

NOTE Confidence: 0.931042349230769

01:01:22.886 --> 01:01:26.560 and account for this more severe disease.

NOTE Confidence: 0.931042349230769

01:01:26.560 --> 01:01:27.955 And again we mimic that

NOTE Confidence: 0.931042349230769

01:01:27.955 --> 01:01:29.350 situation in the mouse here,

NOTE Confidence: 0.931042349230769

01:01:29.350 --> 01:01:31.558 where they now are C model.

NOTE Confidence: 0.931042349230769

01:01:31.560 --> 01:01:34.338 These animals die on average around

NOTE Confidence: 0.931042349230769

01:01:34.340 --> 01:01:37.908 28 days of age and you can see

NOTE Confidence: 0.931042349230769

01:01:37.908 --> 01:01:41.772 by 25 days of age that the 25%

NOTE Confidence: 0.931042349230769

01:01:41.772 --> 01:01:43.676 of the the body weight is made

NOTE Confidence: 0.931042349230769

01:01:43.676 --> 01:01:46.069 up of these very cystic kidneys.

NOTE Confidence: 0.931042349230769

01:01:46.070 --> 01:01:49.486 So again supporting this kind of level

NOTE Confidence: 0.931042349230769

01:01:49.486 --> 01:01:52.157 of policy system being associated

NOTE Confidence: 0.931042349230769

01:01:52.157 --> 01:01:55.487 with the severity of the disease.

NOTE Confidence: 0.931042349230769

01:01:55.490 --> 01:01:57.978 If we look at.

NOTE Confidence: 0.931042349230769

01:01:57.980 --> 01:02:00.555 The level of polycystin expression

NOTE Confidence: 0.931042349230769

01:02:00.555 --> 01:02:02.615 the functional polycystic expression.

NOTE Confidence: 0.931042349230769

01:02:02.620 --> 01:02:05.845 We did this using urinary

NOTE Confidence: 0.931042349230769

01:02:05.845 --> 01:02:07.135 extracellular vesicles,

NOTE Confidence: 0.931042349230769

01:02:07.140 --> 01:02:09.905 which have quite a high level of

NOTE Confidence: 0.931042349230769

01:02:09.905 --> 01:02:12.677 the the the police system protein

NOTE Confidence: 0.931042349230769

01:02:12.677 --> 01:02:15.293 where we can see here in the RC

NOTE Confidence: 0.931042349230769

01:02:15.293 --> 01:02:17.578 model we have a a reduced level

NOTE Confidence: 0.931042349230769

01:02:17.578 --> 01:02:19.559 of the protein to the back.

NOTE Confidence: 0.931042349230769

01:02:19.560 --> 01:02:23.336 40% of the the normal level compared to

NOTE Confidence: 0.931042349230769

01:02:23.336 --> 01:02:27.910 what we we see in the the normal situation.

NOTE Confidence: 0.931042349230769

01:02:27.910 --> 01:02:30.682 So we think that the level of

NOTE Confidence: 0.931042349230769

01:02:30.682 --> 01:02:31.870 the functional protein,

NOTE Confidence: 0.931042349230769

01:02:31.870 --> 01:02:33.240 not the level of expression,

NOTE Confidence: 0.931042349230769

01:02:33.240 --> 01:02:35.845 but a functional and trafficked

NOTE Confidence: 0.931042349230769

01:02:35.845 --> 01:02:38.450 protein is is what's driving

NOTE Confidence: 0.931042349230769

01:02:38.546 --> 01:02:40.718 this more severe disease.

NOTE Confidence: 0.67567700275

01:02:43.610 --> 01:02:47.558 So occasionally we see a digenic

NOTE Confidence: 0.67567700275

01:02:47.558 --> 01:02:51.269 inheritance also in in any PKD.

NOTE Confidence: 0.67567700275

01:02:51.270 --> 01:02:53.178 Your pay is described.

NOTE Confidence: 0.67567700275

01:02:53.178 --> 01:02:55.730 A couple of pedigrees like this,

NOTE Confidence: 0.67567700275

01:02:55.730 --> 01:02:58.318 and this is one from the halt

NOTE Confidence: 0.67567700275

01:02:58.318 --> 01:03:02.326 PKD study from from Rome Peron.

NOTE Confidence: 0.67567700275

01:03:02.330 --> 01:03:05.228 You can see that the individual here

NOTE Confidence: 0.67567700275

01:03:05.228 --> 01:03:08.510 has an inframe deletion of Piketty one,

NOTE Confidence: 0.67567700275

01:03:08.510 --> 01:03:11.033 but a nonsense mutation in P82.

NOTE Confidence: 0.67567700275

01:03:11.033 --> 01:03:14.450 You can see the age at end stage here 43.

NOTE Confidence: 0.67567700275

01:03:14.450 --> 01:03:17.938 Here so 10 to 15 years earlier than

NOTE Confidence: 0.67567700275

01:03:17.938 --> 01:03:20.199 typical for P-81 truncating change.

NOTE Confidence: 0.67567700275

01:03:20.199 --> 01:03:23.440 Can see that the child here at

NOTE Confidence: 0.67567700275

01:03:23.528 --> 01:03:25.892 six months was already had cysts

NOTE Confidence: 0.67567700275

01:03:25.892 --> 01:03:28.759 in the in the in the kidney,

NOTE Confidence: 0.67567700275

01:03:28.760 --> 01:03:31.448 so we think that the combination of these

NOTE Confidence: 0.67567700275

01:03:31.448 --> 01:03:33.620 variants makes the disease more severe,

NOTE Confidence: 0.67567700275

01:03:33.620 --> 01:03:36.002 although not to the early very

NOTE Confidence: 0.67567700275

01:03:36.002 --> 01:03:39.276 early onset we see with the second

NOTE Confidence: 0.67567700275

01:03:39.276 --> 01:03:41.408 hypomorphic PICKITY 1 variant.

NOTE Confidence: 0.67567700275

01:03:41.410 --> 01:03:42.300 And again,

NOTE Confidence: 0.67567700275

01:03:42.300 --> 01:03:45.860 we're able to mimic this type of digenic

NOTE Confidence: 0.67567700275

01:03:45.947 --> 01:03:49.862 inheritance using Steve's Piketty 2 WS,

NOTE Confidence: 0.67567700275

01:03:49.862 --> 01:03:54.868 25 minus model and RP81 RC model.

NOTE Confidence: 0.67567700275

01:03:54.870 --> 01:03:57.010 Both of these by themselves

NOTE Confidence: 0.67567700275

01:03:57.010 --> 01:03:58.722 have rather mild disease,

NOTE Confidence: 0.67567700275

01:03:58.730 --> 01:04:00.410 but if we combine them together,

NOTE Confidence: 0.67567700275

01:04:00.410 --> 01:04:02.462 we see that we have this

NOTE Confidence: 0.67567700275

01:04:02.462 --> 01:04:03.830 much more severe disease.

NOTE Confidence: 0.67567700275

01:04:03.830 --> 01:04:06.550 So we think that the.

NOTE Confidence: 0.67567700275

01:04:06.550 --> 01:04:08.374 The the functional consequence

NOTE Confidence: 0.67567700275

01:04:08.374 --> 01:04:11.110 is of of of of a.

NOTE Confidence: 0.67567700275

01:04:11.110 --> 01:04:13.133 The level of both of these genes

NOTE Confidence: 0.67567700275

01:04:13.133 --> 01:04:15.192 is important to the to the severity

NOTE Confidence: 0.67567700275

01:04:15.192 --> 01:04:16.890 of the disease that we see.

NOTE Confidence: 0.91436376

01:04:19.810 --> 01:04:22.570 And if we look at.

NOTE Confidence: 0.91436376

01:04:22.570 --> 01:04:25.734 Western blot of of these animals with

NOTE Confidence: 0.91436376

01:04:25.734 --> 01:04:27.590 the P-81 and Piketty 2 mutation.

NOTE Confidence: 0.91436376

01:04:27.590 --> 01:04:32.343 If we look at and the situation

NOTE Confidence: 0.91436376

01:04:32.343 --> 01:04:36.220 normally this is the the the.

NOTE Confidence: 0.91436376

01:04:36.220 --> 01:04:38.490 This is the mature form

NOTE Confidence: 0.91436376

01:04:38.490 --> 01:04:40.760 of of polycystin 1 here.

NOTE Confidence: 0.91436376

01:04:40.760 --> 01:04:43.680 This is the immature form of photosystem one.

NOTE Confidence: 0.91436376

01:04:43.680 --> 01:04:46.578 We went for use and OH is cut down

NOTE Confidence: 0.91436376

01:04:46.578 --> 01:04:49.660 to a smaller form and this is PNG's

NOTE Confidence: 0.91436376

01:04:49.660 --> 01:04:52.460 here removing all of the sugars and

NOTE Confidence: 0.91436376

01:04:52.460 --> 01:04:55.457 the see if we look at peak 82 now

NOTE Confidence: 0.91436376

01:04:55.457 --> 01:04:58.242 sells or we see that we don't see

NOTE Confidence: 0.91436376

01:04:58.242 --> 01:05:00.760 this mature form of of police system

NOTE Confidence: 0.91436376

01:05:00.760 --> 01:05:03.640 and one so police system one is not

NOTE Confidence: 0.91436376

01:05:03.720 --> 01:05:06.366 able to traffic and mature properly.

NOTE Confidence: 0.91436376

01:05:06.370 --> 01:05:09.646 D2 is is not present and if we lower

NOTE Confidence: 0.91436376

01:05:09.646 --> 01:05:12.350 the level of P82 to half the level,

NOTE Confidence: 0.91436376

01:05:12.350 --> 01:05:14.968 we see a reduced level by about

NOTE Confidence: 0.91436376

01:05:14.970 --> 01:05:17.938 25% of the the mature form of

NOTE Confidence: 0.91436376

01:05:17.938 --> 01:05:20.869 the the the polycystin one.

NOTE Confidence: 0.91436376

01:05:20.870 --> 01:05:23.939 If we add in this RC Elio here we

NOTE Confidence: 0.91436376

01:05:23.939 --> 01:05:26.134 further lower this mature level

NOTE Confidence: 0.91436376

01:05:26.134 --> 01:05:28.780 and the situation is a little

NOTE Confidence: 0.91436376

01:05:28.870 --> 01:05:30.870 bit complicated here because

NOTE Confidence: 0.91436376

01:05:30.870 --> 01:05:33.870 the RC allele also inhibits the

NOTE Confidence: 0.91436376

01:05:33.870 --> 01:05:36.048 the the normal cleavage of the.

NOTE Confidence: 0.91436376

01:05:36.050 --> 01:05:38.717 Phone system protein at this point here,

NOTE Confidence: 0.91436376

01:05:38.720 --> 01:05:41.015 so we see more of the the full length,

NOTE Confidence: 0.91436376

01:05:41.020 --> 01:05:43.524 which we also think is is not a

NOTE Confidence: 0.91436376

01:05:43.524 --> 01:05:45.365 functional form of other polar

NOTE Confidence: 0.91436376

01:05:45.365 --> 01:05:46.889 system in this situation.

NOTE Confidence: 0.724874363

01:05:50.050 --> 01:05:52.684 So we've used this interaction between

NOTE Confidence: 0.724874363

01:05:52.684 --> 01:05:55.544 policies and one and policies and two

NOTE Confidence: 0.724874363

01:05:55.544 --> 01:05:58.421 to develop and and in vivo in vitro

NOTE Confidence: 0.724874363

01:05:58.421 --> 01:06:01.235 assay to assay different variants to see

NOTE Confidence: 0.724874363

01:06:01.235 --> 01:06:05.160 if they are likely to be pathogenic.

NOTE Confidence: 0.724874363

01:06:05.160 --> 01:06:08.538 So here was expressing these are

NOTE Confidence: 0.724874363

01:06:08.538 --> 01:06:11.338 expressing full length constructs which

NOTE Confidence: 0.724874363

01:06:11.338 --> 01:06:13.858 are tagged full length policy system,

NOTE Confidence: 0.724874363

01:06:13.858 --> 01:06:16.660 one for full length policy system two

NOTE Confidence: 0.724874363

01:06:16.660 --> 01:06:18.865 and then if we express them together

NOTE Confidence: 0.724874363

01:06:18.865 --> 01:06:21.277 we can see we find this surface

NOTE Confidence: 0.724874363

01:06:21.277 --> 01:06:23.339 localized form of a police system.

NOTE Confidence: 0.724874363

01:06:23.339 --> 01:06:26.131 So if we measure this level of of

NOTE Confidence: 0.724874363

01:06:26.131 --> 01:06:28.856 surface policy system one it gives us

NOTE Confidence: 0.724874363

01:06:28.856 --> 01:06:31.496 an indication of whether the the variant

NOTE Confidence: 0.724874363

01:06:31.496 --> 01:06:34.514 we're looking at is able to fold and traffic.

NOTE Confidence: 0.724874363

01:06:34.514 --> 01:06:37.010 That to the surface of the cell and

NOTE Confidence: 0.724874363

01:06:37.075 --> 01:06:39.467 we're kind of using the surface of the

NOTE Confidence: 0.724874363

01:06:39.467 --> 01:06:42.392 cell as a surrogate here for for the

NOTE Confidence: 0.724874363

01:06:42.392 --> 01:06:44.650 ciliary localization of these proteins.

NOTE Confidence: 0.87055269125

01:06:46.810 --> 01:06:50.154 If we look at variants that are either

NOTE Confidence: 0.87055269125

01:06:50.154 --> 01:06:52.847 truncating or strongly predicted to

NOTE Confidence: 0.87055269125

01:06:52.847 --> 01:06:56.015 be pathogenic changes, we don't see

NOTE Confidence: 0.87055269125

01:06:56.015 --> 01:06:58.805 much as surplus police system one.

NOTE Confidence: 0.87055269125

01:06:58.810 --> 01:07:01.130 These are some of the weaker variants and

NOTE Confidence: 0.87055269125

01:07:01.130 --> 01:07:03.766 I said right showed you earlier and they

NOTE Confidence: 0.87055269125

01:07:03.766 --> 01:07:06.128 kind of dividing into two groups here,

NOTE Confidence: 0.87055269125

01:07:06.130 --> 01:07:09.007 ones that seem to be fully inactivating

NOTE Confidence: 0.87055269125

01:07:09.007 --> 01:07:11.907 one and ones that seem to be much

NOTE Confidence: 0.87055269125

01:07:11.907 --> 01:07:14.128 weaker and have a a significant

NOTE Confidence: 0.87055269125

01:07:14.128 --> 01:07:16.898 level of surface polycystin 1.

NOTE Confidence: 0.87055269125

01:07:16.900 --> 01:07:18.856 Some of these are splicing mutations,

NOTE Confidence: 0.87055269125

01:07:18.860 --> 01:07:22.289 so this is a maybe explain it or explaining

NOTE Confidence: 0.87055269125

01:07:22.289 --> 01:07:25.275 why these don't seem to be altered.

NOTE Confidence: 0.87055269125

01:07:25.280 --> 01:07:29.762 If we look at the some of the potential

NOTE Confidence: 0.87055269125

01:07:29.762 --> 01:07:32.314 hypomorphic alleles like the R3277C,

NOTE Confidence: 0.87055269125

01:07:32.314 --> 01:07:35.466 we can see that the level of surface

NOTE Confidence: 0.87055269125

01:07:35.466 --> 01:07:38.795 localization of that is is somewhere again

NOTE Confidence: 0.87055269125

01:07:38.795 --> 01:07:40.703 intermediate between fully inactivating

NOTE Confidence: 0.87055269125

01:07:40.777 --> 01:07:43.059 and and the wild type level here,

NOTE Confidence: 0.87055269125

01:07:43.060 --> 01:07:44.980 so that at a lower level we can

NOTE Confidence: 0.87055269125

01:07:44.980 --> 01:07:46.600 see that for some of these.

NOTE Confidence: 0.87055269125

01:07:46.600 --> 01:07:50.780 Other hypomorphic marker variance.

NOTE Confidence: 0.82312309

01:07:54.520 --> 01:07:55.940 If we so this is,

NOTE Confidence: 0.82312309

01:07:55.940 --> 01:07:58.766 I think this data is showing that a lot

NOTE Confidence: 0.82312309

01:07:58.766 --> 01:08:01.557 of polycystin one and two variants,

NOTE Confidence: 0.82312309

01:08:01.560 --> 01:08:04.956 even if they're even if they're

NOTE Confidence: 0.82312309

01:08:04.956 --> 01:08:08.059 missense changes are are actually

NOTE Confidence: 0.82312309

01:08:08.059 --> 01:08:12.475 folding and trafficking mutations and and,

NOTE Confidence: 0.82312309

01:08:12.480 --> 01:08:15.168 and the reason that they're they're non

NOTE Confidence: 0.82312309

01:08:15.168 --> 01:08:17.738 functional is because that they don't

NOTE Confidence: 0.82312309

01:08:17.738 --> 01:08:19.538 fold and trafficker appropriately.

NOTE Confidence: 0.82312309

01:08:19.540 --> 01:08:21.742 Interestingly, if we treat the cells

NOTE Confidence: 0.82312309

01:08:21.742 --> 01:08:24.751 at a lower level at 30 degrees, so.

NOTE Confidence: 0.82312309

01:08:24.751 --> 01:08:28.188 Give more chance for these these the

NOTE Confidence: 0.82312309

01:08:28.188 --> 01:08:31.383 protein to fold and traffic we can

NOTE Confidence: 0.82312309

01:08:31.383 --> 01:08:35.718 see that for a start the level of a

NOTE Confidence: 0.82312309

01:08:35.718 --> 01:08:38.780 surplus polycystin one is a wild type.

NOTE Confidence: 0.82312309

01:08:38.780 --> 01:08:42.092 It is increased and you can see

NOTE Confidence: 0.82312309

01:08:42.092 --> 01:08:44.170 for a lot of other variants that

NOTE Confidence: 0.82312309

01:08:44.170 --> 01:08:45.705 we see within the gene,

NOTE Confidence: 0.82312309

01:08:45.710 --> 01:08:47.990 including some that are strongly

NOTE Confidence: 0.82312309

01:08:47.990 --> 01:08:50.195 predicted to be pathogenic.

NOTE Confidence: 0.82312309

01:08:50.195 --> 01:08:55.205 We see then some surface protein.

NOTE Confidence: 0.82312309

01:08:55.210 --> 01:08:57.472 From these and also the same

NOTE Confidence: 0.82312309

01:08:57.472 --> 01:08:59.770 for policies in two variants,

NOTE Confidence: 0.82312309

01:08:59.770 --> 01:09:01.894 some maintain and completely

NOTE Confidence: 0.82312309

01:09:01.894 --> 01:09:03.487 inactivated if we.

NOTE Confidence: 0.82312309

01:09:03.490 --> 01:09:05.098 If we use this lower temperature

NOTE Confidence: 0.82312309

01:09:05.098 --> 01:09:07.121 for the level of police system two

NOTE Confidence: 0.82312309

01:09:07.121 --> 01:09:08.909 is increased and the wild type,

NOTE Confidence: 0.82312309

01:09:08.910 --> 01:09:10.640 but also some other variants.

NOTE Confidence: 0.82312309

01:09:10.640 --> 01:09:13.853 So this suggests to us that a

NOTE Confidence: 0.82312309

01:09:13.853 --> 01:09:16.233 chaperone type treatment that enables

NOTE Confidence: 0.82312309

01:09:16.233 --> 01:09:18.987 the policy system one in particular

NOTE Confidence: 0.82312309

01:09:18.987 --> 01:09:21.859 to to fold more efficiently.

NOTE Confidence: 0.82312309

01:09:21.860 --> 01:09:25.024 May be a useful therapy for some

NOTE Confidence: 0.82312309

01:09:25.024 --> 01:09:27.140 patients with missing changes,

NOTE Confidence: 0.82312309

01:09:27.140 --> 01:09:29.898 and since the level of wild type

NOTE Confidence: 0.82312309

01:09:29.898 --> 01:09:32.437 polar system one is also increased

NOTE Confidence: 0.82312309

01:09:32.437 --> 01:09:34.895 and I think that there's evidence

NOTE Confidence: 0.82312309

01:09:34.895 --> 01:09:37.774 that wild type polar system one may

NOTE Confidence: 0.82312309

01:09:37.774 --> 01:09:40.084 be also important within the within

NOTE Confidence: 0.82312309

01:09:40.084 --> 01:09:42.901 the kidney and the ad PKD kidney that

NOTE Confidence: 0.82312309

01:09:42.901 --> 01:09:45.435 this may be helpful even in patients

NOTE Confidence: 0.82312309

01:09:45.435 --> 01:09:47.865 with a with a truncating variant.

NOTE Confidence: 0.80017193125

01:09:51.140 --> 01:09:54.388 We can also get complex alleles in in.

NOTE Confidence: 0.80017193125

01:09:54.390 --> 01:09:58.002 This is a situation where we have

NOTE Confidence: 0.80017193125

01:09:58.002 --> 01:10:00.295 more more than one variant insist

NOTE Confidence: 0.80017193125

01:10:00.295 --> 01:10:03.029 that is a that is generating the

NOTE Confidence: 0.80017193125

01:10:03.029 --> 01:10:05.669 the pathogenic allele and we can

NOTE Confidence: 0.80017193125

01:10:05.669 --> 01:10:08.478 see three different variants here,

NOTE Confidence: 0.80017193125

01:10:08.480 --> 01:10:12.414 including our favorite, our 3277C,

NOTE Confidence: 0.80017193125

01:10:12.414 --> 01:10:15.172 and we can see that was found

NOTE Confidence: 0.80017193125

01:10:15.172 --> 01:10:18.250 in two different families here.

NOTE Confidence: 0.80017193125

01:10:18.250 --> 01:10:20.510 Conceived from the segregation that

NOTE Confidence: 0.80017193125

01:10:20.510 --> 01:10:23.250 they're insists rather than in trans,

NOTE Confidence: 0.80017193125

01:10:23.250 --> 01:10:25.975 and these patients have fairly

NOTE Confidence: 0.80017193125

01:10:25.975 --> 01:10:27.610 typical AD PKD.

NOTE Confidence: 0.80017193125

01:10:27.610 --> 01:10:29.698 Although we know that this variant

NOTE Confidence: 0.80017193125

01:10:29.698 --> 01:10:32.423 by itself only leads to just a few

NOTE Confidence: 0.80017193125

01:10:32.423 --> 01:10:34.003 cents developing in the kidney.

NOTE Confidence: 0.80017193125

01:10:34.010 --> 01:10:36.166 Again, if we look at the level

NOTE Confidence: 0.80017193125

01:10:36.166 --> 01:10:37.769 of surface policies to 1 here,

NOTE Confidence: 0.80017193125

123

01:10:37.770 --> 01:10:39.670 you can see that that's

NOTE Confidence: 0.80017193125

01:10:39.670 --> 01:10:41.722 significantly reduced to the R3277C.

NOTE Confidence: 0.80017193125

01:10:41.722 --> 01:10:44.276 The other two variants reduced,

NOTE Confidence: 0.80017193125

01:10:44.276 --> 01:10:46.406 but to a lesser extent.

NOTE Confidence: 0.80017193125

01:10:46.410 --> 01:10:48.080 But if we look at.

NOTE Confidence: 0.80017193125

01:10:48.080 --> 01:10:49.885 3 variants together or even

NOTE Confidence: 0.80017193125

01:10:49.885 --> 01:10:51.329 two of these variants.

NOTE Confidence: 0.80017193125

01:10:51.330 --> 01:10:53.754 Together we can see this brings it down

NOTE Confidence: 0.80017193125

01:10:53.754 --> 01:10:56.158 to pretty much an inactivating allele,

NOTE Confidence: 0.80017193125

01:10:56.160 --> 01:10:59.088 so that's why we feel that these patients

NOTE Confidence: 0.80017193125

01:10:59.088 --> 01:11:02.190 have a a typical ADP KD presentation.

NOTE Confidence: 0.799546265

01:11:04.890 --> 01:11:09.228 So this brings us to our thought that a

NOTE Confidence: 0.799546265

01:11:09.228 --> 01:11:13.542 PKD is a a dosage related disorder that

NOTE Confidence: 0.799546265

01:11:13.542 --> 01:11:16.358 the level of functional policies to one is

NOTE Confidence: 0.799546265

01:11:16.358 --> 01:11:18.747 important for the severity of the disease.

NOTE Confidence: 0.799546265

01:11:18.750 --> 01:11:20.715 If we have one inactivating

NOTE Confidence: 0.799546265

01:11:20.715 --> 01:11:22.858 allele about a 50% reduction,

NOTE Confidence: 0.799546265

01:11:22.858 --> 01:11:26.266 we get this adult onset disease.

NOTE Confidence: 0.799546265

01:11:26.270 --> 01:11:28.265 If we add on a hypomorphic allele,

NOTE Confidence: 0.799546265

01:11:28.270 --> 01:11:30.310 we can have more severe disease.

NOTE Confidence: 0.799546265

01:11:30.310 --> 01:11:33.660 The hypomorphic allele by itself.

NOTE Confidence: 0.799546265

01:11:33.660 --> 01:11:35.276 Results in milder disease.

NOTE Confidence: 0.799546265

01:11:35.276 --> 01:11:37.700 Then we can have some variants

NOTE Confidence: 0.799546265

01:11:37.779 --> 01:11:39.199 that fit in between,

NOTE Confidence: 0.799546265

01:11:39.200 --> 01:11:40.720 so although they're petty,

NOTE Confidence: 0.799546265

01:11:40.720 --> 01:11:42.620 one variance the disease can

NOTE Confidence: 0.799546265

01:11:42.620 --> 01:11:44.398 be more like PKD 2.

NOTE Confidence: 0.799546265

01:11:44.398 --> 01:11:46.612 That doesn't mean that there's not

NOTE Confidence: 0.799546265

01:11:46.612 --> 01:11:49.503 a lot of other stochastic germline

NOTE Confidence: 0.799546265

01:11:49.503 --> 01:11:52.093 and somatic genetic variants that

NOTE Confidence: 0.799546265

01:11:52.093 --> 01:11:55.192 are in kidney damage that are also

NOTE Confidence: 0.799546265

01:11:55.192 --> 01:11:57.852 modifying the way that the the

NOTE Confidence: 0.799546265

01:11:57.852 --> 01:11:59.836 disease presents and progresses.

NOTE Confidence: 0.707868942857143

01:12:03.500 --> 01:12:07.196 So there's other forms of a PKD.

NOTE Confidence: 0.707868942857143

01:12:07.200 --> 01:12:08.670 This is H and F1,

NOTE Confidence: 0.707868942857143

01:12:08.670 --> 01:12:11.094 beta associated kidney disease,

NOTE Confidence: 0.707868942857143

01:12:11.094 --> 01:12:15.301 which can also result in an ADP

NOTE Confidence: 0.707868942857143

01:12:15.301 --> 01:12:18.535 KD phenotype with H and F1 beta.

NOTE Confidence: 0.707868942857143

01:12:18.540 --> 01:12:20.828 We we see that we have a wide

NOTE Confidence: 0.707868942857143

01:12:20.828 --> 01:12:23.070 range of different phenotypes,

NOTE Confidence: 0.707868942857143

01:12:23.070 --> 01:12:26.706 so as a transcription factor modulating

NOTE Confidence: 0.707868942857143

01:12:26.706 --> 01:12:29.336 the expression of many genes,

NOTE Confidence: 0.707868942857143

01:12:29.340 --> 01:12:31.164 including ones associated

NOTE Confidence: 0.707868942857143

01:12:31.164 --> 01:12:34.204 with PKD one or with.

NOTE Confidence: 0.707868942857143

01:12:34.210 --> 01:12:36.954 A arpkd, but in some cases we can

NOTE Confidence: 0.707868942857143

01:12:36.954 --> 01:12:39.097 find a presentation that really

NOTE Confidence: 0.707868942857143

01:12:39.097 --> 01:12:42.825 mimics what we see in in 80P KD

NOTE Confidence: 0.707868942857143

01:12:42.825 --> 01:12:45.549 with multiple cysts in the kidney,

NOTE Confidence: 0.707868942857143

01:12:45.550 --> 01:12:49.590 but are rather limited other phenotypes.

NOTE Confidence: 0.846094315

01:12:52.440 --> 01:12:56.436 So a few years ago we published a paper

NOTE Confidence: 0.846094315

01:12:56.436 --> 01:12:59.052 saying there was a number of paper

NOTE Confidence: 0.846094315

01:12:59.052 --> 01:13:01.340 number of families that were published

NOTE Confidence: 0.846094315

01:13:01.340 --> 01:13:04.220 in the 1990s that suggested that

NOTE Confidence: 0.846094315

01:13:04.220 --> 01:13:07.214 there were unlinked to P-81 and P82.

NOTE Confidence: 0.846094315

01:13:07.214 --> 01:13:10.280 So suggesting there may be other genes

NOTE Confidence: 0.846094315

01:13:10.370 --> 01:13:13.490 for for a PKD we found in four out of

NOTE Confidence: 0.846094315

01:13:13.575 --> 01:13:17.079 five of these families that if we look

NOTE Confidence: 0.846094315

01:13:17.079 --> 01:13:19.732 carefully for the pathogenic variant and

NOTE Confidence: 0.846094315

01:13:19.732 --> 01:13:22.850 beginning one and Piketty 2 and also.

NOTE Confidence: 0.846094315

01:13:22.850 --> 01:13:25.535 I revisited the linkage sometimes

NOTE Confidence: 0.846094315

01:13:25.535 --> 01:13:27.683 with newly collected samples,

NOTE Confidence: 0.846094315

01:13:27.690 --> 01:13:30.230 we could show that.

NOTE Confidence: 0.846094315

01:13:30.230 --> 01:13:31.847 And most of them were either Piketty,

NOTE Confidence: 0.846094315

01:13:31.850 --> 01:13:33.482 one or Piketty 2,

NOTE Confidence: 0.846094315

01:13:33.482 --> 01:13:36.930 although there was one that was unresolved.

NOTE Confidence: 0.846094315

01:13:36.930 --> 01:13:39.468 We said maybe prep rather prematurely

NOTE Confidence: 0.846094315

01:13:39.468 --> 01:13:42.507 at that stage that this reanalysis does

NOTE Confidence: 0.846094315

01:13:42.507 --> 01:13:45.468 not support the the existence of a.

NOTE Confidence: 0.846094315

01:13:45.470 --> 01:13:47.510 P-83 and and as we know,

NOTE Confidence: 0.846094315

01:13:47.510 --> 01:13:50.107 since that time there's been several genes

NOTE Confidence: 0.846094315

01:13:50.107 --> 01:13:53.538 that are mimic the the AD PKD phenotype.

NOTE Confidence: 0.753784392625

01:13:56.290 --> 01:13:59.104 So from work from Steve's group

NOTE Confidence: 0.753784392625

01:13:59.104 --> 01:14:02.345 and Josh Drents Group A different

NOTE Confidence: 0.753784392625

01:14:02.345 --> 01:14:05.530 disease that AutoZone will dominant

NOTE Confidence: 0.753784392625

01:14:05.530 --> 01:14:08.241 polycystic liver disease is due

NOTE Confidence: 0.753784392625

01:14:08.241 --> 01:14:10.350 to either PRK or the major LOCI,

NOTE Confidence: 0.753784392625

01:14:10.350 --> 01:14:13.662 or PRK, CSH and and sex 63.

NOTE Confidence: 0.753784392625

01:14:13.662 --> 01:14:15.846 We're going to see the presentation here.

NOTE Confidence: 0.753784392625

01:14:15.850 --> 01:14:19.329 A very large liver but rather limited

NOTE Confidence: 0.753784392625

01:14:19.329 --> 01:14:22.609 cyst within the within the kidney,

NOTE Confidence: 0.753784392625

01:14:22.610 --> 01:14:24.666 and these proteins are

NOTE Confidence: 0.753784392625

01:14:24.666 --> 01:14:26.208 involved in trafficking.

NOTE Confidence: 0.753784392625

01:14:26.210 --> 01:14:29.390 Or glycosylation unfolding and

NOTE Confidence: 0.753784392625

01:14:29.390 --> 01:14:33.365 quality control of a membrane

NOTE Confidence: 0.753784392625

01:14:33.365 --> 01:14:35.330 and and secreted proteins.

NOTE Confidence: 0.753784392625

01:14:35.330 --> 01:14:38.060 And it seems like a polar system.

NOTE Confidence: 0.753784392625

01:14:38.060 --> 01:14:39.792 One is particularly vulnerable

NOTE Confidence: 0.753784392625

01:14:39.792 --> 01:14:42.390 to a defects in this pathway.

NOTE Confidence: 0.863205862222222

01:14:44.760 --> 01:14:46.800 We did some whole exome sequencing

NOTE Confidence: 0.863205862222222

01:14:46.800 --> 01:14:49.631 a number of years ago on a rather

NOTE Confidence: 0.863205862222222

01:14:49.631 --> 01:14:51.035 limited number of families.

NOTE Confidence: 0.863205862222222

01:14:51.040 --> 01:14:53.168 I I was somewhat skeptical that there

NOTE Confidence: 0.863205862222222

01:14:53.168 --> 01:14:55.460 was other genes for 80 PKD at the time,

NOTE Confidence: 0.863205862222222

01:14:55.460 --> 01:14:57.675 but the postdoc during the

NOTE Confidence: 0.863205862222222

01:14:57.675 --> 01:14:59.447 study was very persistent.

NOTE Confidence: 0.863205862222222

01:14:59.450 --> 01:15:03.573 We found a missense change in Ghana

NOTE Confidence: 0.863205862222222

01:15:03.573 --> 01:15:07.369 hub here in in one patient with a

NOTE Confidence: 0.863205862222222

01:15:07.369 --> 01:15:10.050 cyst within the kidney and also a

NOTE Confidence: 0.863205862222222

01:15:10.132 --> 01:15:13.205 cyst within the the liver in the

NOTE Confidence: 0.863205862222222

01:15:13.205 --> 01:15:15.480 two individuals within the family.

NOTE Confidence: 0.863205862222222

01:15:15.480 --> 01:15:16.900 She is a missense change.

NOTE Confidence: 0.863205862222222

01:15:16.900 --> 01:15:19.690 It was difficult to know whether

NOTE Confidence: 0.863205862222222

01:15:19.690 --> 01:15:21.085 it was significant,

NOTE Confidence: 0.863205862222222

01:15:21.090 --> 01:15:24.429 but this was a great candidate because

NOTE Confidence: 0.863205862222222

01:15:24.430 --> 01:15:26.626 it was the binding partner here

NOTE Confidence: 0.863205862222222

01:15:26.626 --> 01:15:29.413 the glucose stays out for subunit.

NOTE Confidence: 0.863205862222222

01:15:29.413 --> 01:15:32.779 Here binding with the glycosidase fetus.

NOTE Confidence: 0.863205862222222

01:15:32.780 --> 01:15:34.622 So obviously a great candidate and

NOTE Confidence: 0.863205862222222

01:15:34.622 --> 01:15:36.777 by going on and doing sequencing

NOTE Confidence: 0.863205862222222

01:15:36.777 --> 01:15:38.067 of other families,

NOTE Confidence: 0.863205862222222

01:15:38.070 --> 01:15:41.382 we were able to find other families with ADP,

NOTE Confidence: 0.863205862222222

01:15:41.390 --> 01:15:45.796 KD and AD. PLD has has Whitney.

NOTE Confidence: 0.863205862222222

01:15:45.796 --> 01:15:51.610 Let's see here in the associated with a PLD.

NOTE Confidence: 0.863205862222222

01:15:51.610 --> 01:15:53.998 If we look at ourselves that

NOTE Confidence: 0.863205862222222

01:15:53.998 --> 01:15:56.530 don't have a again and again,

NOTE Confidence: 0.863205862222222

01:15:56.530 --> 01:15:59.440 we see that the policy system

NOTE Confidence: 0.863205862222222

01:15:59.440 --> 01:16:02.900 mature form is not really a found

NOTE Confidence: 0.863205862222222

01:16:02.900 --> 01:16:05.301 and this is kind of in contrast

NOTE Confidence: 0.863205862222222

01:16:05.301 --> 01:16:08.104 what we see with some other control

NOTE Confidence: 0.863205862222222

01:16:08.104 --> 01:16:11.062 proteins where we see the the the

NOTE Confidence: 0.863205862222222

01:16:11.062 --> 01:16:13.228 level that is that is not mature.

NOTE Confidence: 0.863205862222222

01:16:13.228 --> 01:16:16.380 It is only a small part of the total amount

NOTE Confidence: 0.863205862222222

01:16:16.380 --> 01:16:19.229 of protein compared to to polar system one.

NOTE Confidence: 0.863205862222222

01:16:19.230 --> 01:16:22.026 And even in the heterozygous phenotypes.

NOTE Confidence: 0.863205862222222

01:16:22.030 --> 01:16:23.980 So the phenotype that we're

NOTE Confidence: 0.863205862222222

01:16:23.980 --> 01:16:25.540 seeing here in patients,

NOTE Confidence: 0.863205862222222

01:16:25.540 --> 01:16:28.591 we can see that the the level of the

NOTE Confidence: 0.863205862222222

01:16:28.591 --> 01:16:31.814 the mature form of the the the policy

NOTE Confidence: 0.863205862222222

01:16:31.814 --> 01:16:34.879 system one is is already decreased.

NOTE Confidence: 0.863205862222222

01:16:34.880 --> 01:16:38.080 And if we look at scanner negative cells,

NOTE Confidence: 0.863205862222222

01:16:38.080 --> 01:16:40.096 we can see that police system two

NOTE Confidence: 0.863205862222222

01:16:40.096 --> 01:16:41.860 that's normally found on the stellium.

NOTE Confidence: 0.863205862222222

01:16:41.860 --> 01:16:44.856 We didn't find localised to the cilium

NOTE Confidence: 0.863205862222222

01:16:44.856 --> 01:16:47.844 in these neural cells, so as I say,

NOTE Confidence: 0.863205862222222

01:16:47.844 --> 01:16:49.274 it seems that polar system,

NOTE Confidence: 0.863205862222222

01:16:49.280 --> 01:16:51.408 one in particular is.

NOTE Confidence: 0.7716242876

01:16:53.430 --> 01:16:56.664 Is primed or is particularly susceptible

NOTE Confidence: 0.7716242876

01:16:56.664 --> 01:16:58.820 to folding defects associated

NOTE Confidence: 0.7716242876

01:16:58.904 --> 01:17:01.139 with defects in this pathway?

NOTE Confidence: 0.52897483

01:17:03.180 --> 01:17:08.070 So Whitney again published a couple

NOTE Confidence: 0.52897483

01:17:08.070 --> 01:17:10.100 of years ago or several years ago.

NOTE Confidence: 0.52897483

01:17:10.100 --> 01:17:14.572 Now that LG eight was a also a

NOTE Confidence: 0.52897483

01:17:14.572 --> 01:17:18.088 form of polycystic liver disease,

NOTE Confidence: 0.52897483

01:17:18.088 --> 01:17:20.776 and we think that the phenotype is

NOTE Confidence: 0.52897483

01:17:20.776 --> 01:17:23.490 not only a polycystic liver but

NOTE Confidence: 0.52897483

01:17:23.490 --> 01:17:25.740 also of polycystic kidney disease.

NOTE Confidence: 0.52897483

01:17:25.740 --> 01:17:28.812 This is a a family here with three

NOTE Confidence: 0.52897483

01:17:28.812 --> 01:17:30.639 affected individuals who can see

NOTE Confidence: 0.52897483

01:17:30.639 --> 01:17:32.935 that they have cysts in the kidney,

NOTE Confidence: 0.52897483

01:17:32.940 --> 01:17:36.190 but interestingly. Are the few.

NOTE Confidence: 0.52897483

01:17:36.190 --> 01:17:38.860 This in the in the liver.

NOTE Confidence: 0.52897483

01:17:38.860 --> 01:17:40.798 The cysts the interestingly a lot

NOTE Confidence: 0.52897483

01:17:40.798 --> 01:17:43.462 of the time seemed to be more in the

NOTE Confidence: 0.52897483

01:17:43.462 --> 01:17:45.639 left kidney than the the right kidney,

NOTE Confidence: 0.52897483

01:17:45.640 --> 01:17:47.920 and we're not sure completely

NOTE Confidence: 0.52897483

01:17:47.920 --> 01:17:49.744 sure why that is.

NOTE Confidence: 0.837387792

01:17:52.290 --> 01:17:55.918 The one family from our and that

NOTE Confidence: 0.837387792

01:17:55.918 --> 01:17:58.282 reanalysis of of P-83 families.

NOTE Confidence: 0.837387792

01:17:58.282 --> 01:18:00.262 Hispanic or Spanish family that

NOTE Confidence: 0.837387792

01:18:00.262 --> 01:18:02.349 where we didn't find Piketty,

NOTE Confidence: 0.837387792

01:18:02.350 --> 01:18:03.730 one of Piketty 2 variants,

NOTE Confidence: 0.837387792

01:18:03.730 --> 01:18:07.447 interestingly has an LG 8 variant here,

NOTE Confidence: 0.837387792

01:18:07.450 --> 01:18:09.830 which segregates with the disease,

NOTE Confidence: 0.837387792

01:18:09.830 --> 01:18:12.200 although it indicates that there's

NOTE Confidence: 0.837387792

01:18:12.200 --> 01:18:14.096 another affected individual in

NOTE Confidence: 0.837387792

01:18:14.096 --> 01:18:16.535 the family and this individual on

NOTE Confidence: 0.837387792

01:18:16.535 --> 01:18:19.242 ultrasound has a a couple of cysts

NOTE Confidence: 0.837387792

01:18:19.242 --> 01:18:21.107 within the within the kidney.

NOTE Confidence: 0.837387792

01:18:21.110 --> 01:18:23.096 Interestingly, there's a couple of other.

NOTE Confidence: 0.837387792

01:18:23.100 --> 01:18:25.695 Variance but in in ciliopathy

NOTE Confidence: 0.837387792

01:18:25.695 --> 01:18:29.455 genes which also so these will be

NOTE Confidence: 0.837387792

01:18:29.455 --> 01:18:32.678 recessive variants which are also

NOTE Confidence: 0.837387792

01:18:32.678 --> 01:18:35.366 segregating or partially segregating

NOTE Confidence: 0.837387792

01:18:35.370 --> 01:18:37.350 with the disease in the family.

NOTE Confidence: 0.837387792

01:18:37.350 --> 01:18:39.852 So we think that these other

NOTE Confidence: 0.837387792

01:18:39.852 --> 01:18:42.348 factors may be influencing the

NOTE Confidence: 0.837387792

01:18:42.348 --> 01:18:46.062 severity of the disease and maybe

NOTE Confidence: 0.837387792

01:18:46.062 --> 01:18:49.194 determining whether single a LG 8

NOTE Confidence: 0.837387792

01:18:49.194 --> 01:18:51.888 variants are shown to be pathogenic.

NOTE Confidence: 0.837387792

01:18:51.890 --> 01:18:54.290 If we look at the the families that

NOTE Confidence: 0.837387792

01:18:54.290 --> 01:18:55.889 we've collected with a LG eight,

NOTE Confidence: 0.837387792

01:18:55.890 --> 01:18:59.193 we can see that on the whole they have

NOTE Confidence: 0.837387792

01:18:59.193 --> 01:19:01.972 fairly preserved renal function and a

NOTE Confidence: 0.837387792

01:19:01.972 --> 01:19:07.222 milder than what we expect for PKD 2 and a,

NOTE Confidence: 0.837387792

01:19:07.222 --> 01:19:09.166 LGH LLG nine,

NOTE Confidence: 0.837387792

01:19:09.170 --> 01:19:11.925 which Whitney also described as

NOTE Confidence: 0.837387792

01:19:11.925 --> 01:19:16.409 an AD PKD gene a few years ago.

NOTE Confidence: 0.837387792

01:19:16.410 --> 01:19:19.098 We also found another number of

NOTE Confidence: 0.837387792

01:19:19.098 --> 01:19:21.678 families with this change, and again,

NOTE Confidence: 0.837387792

01:19:21.678 --> 01:19:22.072 the.

NOTE Confidence: 0.837387792

01:19:22.072 --> 01:19:24.830 The the the disease is maybe a

NOTE Confidence: 0.837387792

01:19:24.917 --> 01:19:27.485 little bit more severe on average

NOTE Confidence: 0.837387792

01:19:27.485 --> 01:19:30.399 than we see with with the LGH,

NOTE Confidence: 0.837387792

01:19:30.400 --> 01:19:32.270 although most of the patients

NOTE Confidence: 0.837387792

01:19:32.270 --> 01:19:33.766 have preserved renal function,

NOTE Confidence: 0.837387792

01:19:33.770 --> 01:19:36.032 but obviously some have a decline

NOTE Confidence: 0.837387792

01:19:36.032 --> 01:19:37.960 in in renal function here.

NOTE Confidence: 0.761560978888889

01:19:40.190 --> 01:19:45.291 We did some work with John Sayer of the UK

NOTE Confidence: 0.761560978888889

01:19:45.291 --> 01:19:49.066 Biobank and the genome England 100,000.

NOTE Confidence: 0.761560978888889

01:19:49.066 --> 01:19:51.064 Genome Project England.

NOTE Confidence: 0.761560978888889

01:19:51.064 --> 01:19:54.394 100,000 genomes project and looking

NOTE Confidence: 0.761560978888889

01:19:54.394 --> 01:19:58.446 at the UK Biobank to start with here

NOTE Confidence: 0.761560978888889

01:19:58.446 --> 01:20:01.726 we're looking at patients that have

NOTE Confidence: 0.761560978888889

01:20:01.726 --> 01:20:04.681 a rare variance with truncating

NOTE Confidence: 0.761560978888889

01:20:04.681 --> 01:20:07.007 mutations in this particular gene,

NOTE Confidence: 0.761560978888889

01:20:07.007 --> 01:20:09.660 and then we're looking at the ICD

NOTE Confidence: 0.761560978888889

01:20:09.731 --> 01:20:12.047 codes here for either policy or

NOTE Confidence: 0.761560978888889

01:20:12.047 --> 01:20:14.060 cystic kidney disease or other

NOTE Confidence: 0.761560978888889

01:20:14.060 --> 01:20:16.420 diseases of the kidney, which you,

NOTE Confidence: 0.761560978888889

01:20:16.420 --> 01:20:19.460 which also includes some cysts of the kidney.

NOTE Confidence: 0.761560978888889

01:20:19.460 --> 01:20:22.960 And also you know. Proposed.

NOTE Confidence: 0.761560978888889

01:20:22.960 --> 01:20:24.484 Acquired cystic disease.

NOTE Confidence: 0.761560978888889

01:20:24.484 --> 01:20:25.500 For instance,

NOTE Confidence: 0.761560978888889

01:20:25.500 --> 01:20:28.069 we can see that there's an enrichment

NOTE Confidence: 0.761560978888889

01:20:28.069 --> 01:20:30.322 here in the the cases compared

NOTE Confidence: 0.761560978888889

01:20:30.322 --> 01:20:32.835 to the controls for a LG 8IN.

NOTE Confidence: 0.761560978888889

01:20:32.840 --> 01:20:35.678 In both of these two populations,

NOTE Confidence: 0.761560978888889

01:20:35.680 --> 01:20:39.124 although we can see there's a greater

NOTE Confidence: 0.761560978888889

01:20:39.124 --> 01:20:42.496 enrichment here for a LG nine in the

NOTE Confidence: 0.761560978888889

01:20:42.496 --> 01:20:45.520 the cases compared to the the controls.

NOTE Confidence: 0.761560978888889

01:20:45.520 --> 01:20:48.656 If we look at the Genome Genomics,

NOTE Confidence: 0.761560978888889

01:20:48.660 --> 01:20:51.204 England project and again look at

NOTE Confidence: 0.761560978888889

01:20:51.204 --> 01:20:53.358 loss of function variants compared

NOTE Confidence: 0.761560978888889

01:20:53.358 --> 01:20:55.638 to the to the total alleles,

NOTE Confidence: 0.761560978888889

01:20:55.640 --> 01:20:58.230 we can see that these are again

NOTE Confidence: 0.761560978888889

01:20:58.230 --> 01:21:00.757 enriched in the in the the cases.

NOTE Confidence: 0.761560978888889

01:21:00.760 --> 01:21:03.835 The cystic kidney disease cases

NOTE Confidence: 0.761560978888889

01:21:03.835 --> 01:21:06.952 compared to the to the controls

NOTE Confidence: 0.761560978888889

01:21:06.952 --> 01:21:09.920 here and likewise for a LG 9.

NOTE Confidence: 0.761560978888889

01:21:09.920 --> 01:21:10.372 However,

NOTE Confidence: 0.761560978888889

01:21:10.372 --> 01:21:12.180 these variants are especially

NOTE Confidence: 0.761560978888889

01:21:12.180 --> 01:21:15.549 for a OG eight are quite common.

NOTE Confidence: 0.761560978888889

01:21:15.550 --> 01:21:17.342 Within the the population

NOTE Confidence: 0.761560978888889

01:21:17.342 --> 01:21:18.238 truncating variants,

NOTE Confidence: 0.761560978888889

01:21:18.240 --> 01:21:20.956 so I think that they don't always

NOTE Confidence: 0.761560978888889

01:21:20.956 --> 01:21:24.107 result in a in a cystic phenotype,

NOTE Confidence: 0.761560978888889

01:21:24.110 --> 01:21:27.670 and that may be that we need other

NOTE Confidence: 0.761560978888889

01:21:27.670 --> 01:21:30.209 variants to before we these.

NOTE Confidence: 0.761560978888889

01:21:30.210 --> 01:21:32.890 These diseases are are manifested,

NOTE Confidence: 0.761560978888889

01:21:32.890 --> 01:21:35.284 so we might want to consider these

NOTE Confidence: 0.761560978888889

01:21:35.284 --> 01:21:38.716 more like a maybe a a riskily old than

NOTE Confidence: 0.761560978888889

01:21:38.716 --> 01:21:41.237 a complete monogenic form of of a PKD.

NOTE Confidence: 0.776174080909091

01:21:44.050 --> 01:21:46.582 We also described a few years

NOTE Confidence: 0.776174080909091

01:21:46.582 --> 01:21:48.860 ago with Emily Kornak Gugel.

NOTE Confidence: 0.867299088

01:21:51.550 --> 01:21:54.130 Using whole exome sequencing again,

NOTE Confidence: 0.867299088

01:21:54.130 --> 01:21:57.660 a family which had a a DNA JB 11 variant.

NOTE Confidence: 0.867299088

01:21:57.660 --> 01:22:00.444 So this is a a coach chaperone protein

NOTE Confidence: 0.867299088

01:22:00.444 --> 01:22:03.944 that works with deep in the in the in the

NOTE Confidence: 0.867299088

01:22:03.944 --> 01:22:06.581 Plasmic reticulum and again plays a role

NOTE Confidence: 0.867299088

01:22:06.581 --> 01:22:09.430 in the folding and trafficking of proteins.

NOTE Confidence: 0.867299088

01:22:09.430 --> 01:22:12.790 This time the phenotype is of smaller

NOTE Confidence: 0.867299088

01:22:12.790 --> 01:22:16.468 kidneys with with multiple cysts in them,

NOTE Confidence: 0.867299088

01:22:16.470 --> 01:22:18.282 but in the older individuals we

NOTE Confidence: 0.867299088

01:22:18.282 --> 01:22:20.419 can see we see a decline in.

NOTE Confidence: 0.867299088

01:22:20.420 --> 01:22:22.850 In renal function this missense

NOTE Confidence: 0.867299088

01:22:22.850 --> 01:22:24.576 change again missense change.

NOTE Confidence: 0.867299088

01:22:24.576 --> 01:22:27.460 It difficult to know whether it's pathogenic,

NOTE Confidence: 0.867299088

01:22:27.460 --> 01:22:30.208 but it wasn't a very preserved

NOTE Confidence: 0.867299088

01:22:30.208 --> 01:22:32.780 conserved site within the protein.

NOTE Confidence: 0.867299088

01:22:32.780 --> 01:22:35.685 Again, we're able to go on and

NOTE Confidence: 0.867299088

01:22:35.685 --> 01:22:37.810 find additional families and then

NOTE Confidence: 0.867299088

01:22:37.810 --> 01:22:39.810 Emily recently has published a

NOTE Confidence: 0.867299088

01:22:39.810 --> 01:22:42.416 a wider range of 77 families,

NOTE Confidence: 0.867299088

01:22:42.416 --> 01:22:44.806 77 patients from 27 pedigrees,

NOTE Confidence: 0.867299088

01:22:44.806 --> 01:22:47.895 and we can see that they have a rather

NOTE Confidence: 0.867299088

01:22:47.895 --> 01:22:50.445 consistent phenotype where they have.

NOTE Confidence: 0.867299088

01:22:50.450 --> 01:22:52.682 Preserve renal function and and maybe

NOTE Confidence: 0.867299088

01:22:52.682 --> 01:22:55.379 just a few cysts and without kidney

NOTE Confidence: 0.867299088

01:22:55.379 --> 01:22:58.393 enlargement up until 50 years of age and

NOTE Confidence: 0.867299088

01:22:58.393 --> 01:23:00.994 then we can see we see this decline in

NOTE Confidence: 0.867299088

01:23:01.000 --> 01:23:03.816 renal function so that the age at end

NOTE Confidence: 0.867299088

01:23:03.816 --> 01:23:07.053 stage is similar to what we see in PK 82.

NOTE Confidence: 0.867299088

01:23:07.060 --> 01:23:09.482 In this case the kidneys stay pretty

NOTE Confidence: 0.867299088

01:23:09.482 --> 01:23:11.975 small and become fibrotic and so they

NOTE Confidence: 0.867299088

01:23:11.975 --> 01:23:14.580 look somewhat similar to what we see in.

NOTE Confidence: 0.867299088

01:23:14.580 --> 01:23:17.130 AutoZone will dominant tubular interstitial

NOTE Confidence: 0.867299088

01:23:17.130 --> 01:23:20.498 kidney disease due to you mod or or.

NOTE Confidence: 0.867299088

01:23:20.500 --> 01:23:23.740 Mark one variance.

NOTE Confidence: 0.867299088

01:23:23.740 --> 01:23:26.820 So we can see here where DNA

NOTE Confidence: 0.867299088

01:23:26.820 --> 01:23:29.219 JB 11 is in this.

NOTE Confidence: 0.867299088

01:23:29.220 --> 01:23:32.480 In this pathway involved with

NOTE Confidence: 0.867299088

01:23:32.480 --> 01:23:35.080 folding and trafficking of protein.

NOTE Confidence: 0.867299088

01:23:35.080 --> 01:23:39.798 So this is PRK, CSH and ganap.

NOTE Confidence: 0.867299088

01:23:39.800 --> 01:23:43.922 Here we can see also a variance in a

NOTE Confidence: 0.867299088

01:23:43.922 --> 01:23:47.715 LG 8 and a LG nine. As I mentioned.

NOTE Confidence: 0.867299088

01:23:47.715 --> 01:23:50.830 There's also a variance in PM two

NOTE Confidence: 0.867299088

01:23:50.928 --> 01:23:53.924 that give rise to in a recessive.

NOTE Confidence: 0.867299088

01:23:53.930 --> 01:23:56.680 Way and associated with particular

NOTE Confidence: 0.867299088

01:23:56.680 --> 01:23:59.506 a promoter. Mutations to an AR.

NOTE Confidence: 0.867299088

01:23:59.510 --> 01:24:00.360 PKD phenotype.

NOTE Confidence: 0.867299088

01:24:00.360 --> 01:24:03.335 So we're going to see that there's

NOTE Confidence: 0.867299088

01:24:03.335 --> 01:24:06.218 plenty of variance within this pathway

NOTE Confidence: 0.867299088

01:24:06.218 --> 01:24:10.849 that are associated with a PKD or a PLD

NOTE Confidence: 0.867299088

01:24:10.849 --> 01:24:13.990 phenotype which may be due to the to

NOTE Confidence: 0.867299088

01:24:13.990 --> 01:24:16.150 the susceptibility of of policy system,

NOTE Confidence: 0.867299088

01:24:16.150 --> 01:24:18.999 one to to variance in this pathway.

NOTE Confidence: 0.8689881

01:24:22.590 --> 01:24:23.979 So we also.

NOTE Confidence: 0.756328268571429

01:24:26.140 --> 01:24:29.868 A recently there's been a couple of papers

NOTE Confidence: 0.756328268571429

01:24:29.868 --> 01:24:33.036 to do with biallelic disease associated

NOTE Confidence: 0.756328268571429

01:24:33.036 --> 01:24:37.626 with DNA JB 11 from a Turkish family

NOTE Confidence: 0.756328268571429

01:24:37.626 --> 01:24:42.474 here and also from a a French family.

NOTE Confidence: 0.756328268571429

01:24:42.480 --> 01:24:46.264 We can see that the phenotype in these

NOTE Confidence: 0.756328268571429

01:24:46.264 --> 01:24:50.844 cases is is a severe disease of in utero

NOTE Confidence: 0.756328268571429

01:24:50.844 --> 01:24:54.129 presentation with the cystic kidneys.

NOTE Confidence: 0.756328268571429

01:24:54.130 --> 01:24:57.220 Here assistance also or disorganization

NOTE Confidence: 0.756328268571429

01:24:57.220 --> 01:25:00.310 within the the pancreas of

NOTE Confidence: 0.756328268571429

01:25:00.409 --> 01:25:03.036 fibrosis within the within,

NOTE Confidence: 0.756328268571429

01:25:03.036 --> 01:25:06.420 the within the liver.

NOTE Confidence: 0.756328268571429

01:25:06.420 --> 01:25:09.990 And so we can see.

NOTE Confidence: 0.756328268571429

01:25:09.990 --> 01:25:11.388 And also they looked at the

NOTE Confidence: 0.756328268571429

01:25:11.388 --> 01:25:13.011 cilia in these cases and I don't

NOTE Confidence: 0.756328268571429

01:25:13.011 --> 01:25:14.502 know if you can really see this,

NOTE Confidence: 0.756328268571429

01:25:14.510 --> 01:25:16.750 but this is the the normal size

NOTE Confidence: 0.756328268571429

01:25:16.750 --> 01:25:18.569 cilia here and they're suggesting

NOTE Confidence: 0.756328268571429

01:25:18.569 --> 01:25:21.299 in the in the patients that they

NOTE Confidence: 0.756328268571429

01:25:21.299 --> 01:25:23.650 have longer and torturous cilia.

NOTE Confidence: 0.756328268571429

01:25:23.650 --> 01:25:24.016 Obviously,

NOTE Confidence: 0.756328268571429

01:25:24.016 --> 01:25:26.578 it's a little difficult to tell if

NOTE Confidence: 0.756328268571429

01:25:26.578 --> 01:25:29.048 this is true from this analysis,

NOTE Confidence: 0.756328268571429

01:25:29.050 --> 01:25:32.410 but it does indicate that we get a

NOTE Confidence: 0.756328268571429

01:25:32.410 --> 01:25:36.067 a more syndromic type of ciliopathy

NOTE Confidence: 0.756328268571429

01:25:36.067 --> 01:25:40.540 phenotypes associated with the DNA JB 11.

NOTE Confidence: 0.756328268571429

01:25:40.540 --> 01:25:43.095 Suggesting or asking the question

NOTE Confidence: 0.756328268571429

01:25:43.095 --> 01:25:45.650 of whether it's more generally

NOTE Confidence: 0.756328268571429

01:25:45.733 --> 01:25:48.209 involved in asilia development.

NOTE Confidence: 0.715435431428571

01:25:51.250 --> 01:25:55.135 Recently we identified 1 monoallelic

NOTE Confidence: 0.715435431428571

01:25:55.135 --> 01:25:59.240 variants in FT 140 as a cause

NOTE Confidence: 0.715435431428571

01:25:59.240 --> 01:26:03.360 of an ADP KD light phenotype.

NOTE Confidence: 0.715435431428571

01:26:03.360 --> 01:26:04.848 As you know, I have T,

NOTE Confidence: 0.715435431428571

01:26:04.850 --> 01:26:07.450 as is intracellular transport process.

NOTE Confidence: 0.715435431428571

01:26:07.450 --> 01:26:10.831 That's important for moving proteins in and

NOTE Confidence: 0.715435431428571

01:26:10.831 --> 01:26:15.330 out of the cilium and generating the cilium.

NOTE Confidence: 0.715435431428571

01:26:15.330 --> 01:26:18.471 This is the I FT140 as part of the

NOTE Confidence: 0.715435431428571

01:26:18.471 --> 01:26:22.530 IFA complex, which is a thought to be

NOTE Confidence: 0.715435431428571

01:26:22.530 --> 01:26:25.470 associated particularly with the retrograde.

NOTE Confidence: 0.715435431428571

01:26:25.470 --> 01:26:28.260 IFT transport and by allelic

NOTE Confidence: 0.715435431428571

01:26:28.260 --> 01:26:31.776 variants here are associated with a

NOTE Confidence: 0.715435431428571

01:26:31.776 --> 01:26:34.296 more severe ciliopathy phenotype.

NOTE Confidence: 0.715435431428571

01:26:34.300 --> 01:26:37.015 Short rib thoratic displays Asia

NOTE Confidence: 0.715435431428571

01:26:37.015 --> 01:26:40.326 which also has a cystic kidneys

NOTE Confidence: 0.715435431428571

01:26:40.326 --> 01:26:43.314 as as part of its phenotype.

NOTE Confidence: 0.715435431428571

01:26:43.320 --> 01:26:46.596 We were able to identify rather large

NOTE Confidence: 0.715435431428571

01:26:46.600 --> 01:26:49.798 #38 families and 59 affected individuals

NOTE Confidence: 0.715435431428571

01:26:49.798 --> 01:26:52.980 that had variants in in FT 140.

NOTE Confidence: 0.715435431428571

01:26:52.980 --> 01:26:55.710 We know from work from Greg buzzer

NOTE Confidence: 0.715435431428571

01:26:55.710 --> 01:26:58.860 that if this protein or this gene is

NOTE Confidence: 0.715435431428571

01:26:58.860 --> 01:27:02.414 is knocked out in the kidney then we

NOTE Confidence: 0.715435431428571

01:27:02.414 --> 01:27:04.739 get a polycystic kidney phenotype.

NOTE Confidence: 0.903299264285715

01:27:07.010 --> 01:27:09.980 We can see again that we have a fairly

NOTE Confidence: 0.903299264285715

01:27:09.980 --> 01:27:12.228 distinctive phenotype in these patients,

NOTE Confidence: 0.903299264285715

01:27:12.230 --> 01:27:15.494 but this time it's just a small number

NOTE Confidence: 0.903299264285715

01:27:15.494 --> 01:27:18.520 of rather large cities that we see.

NOTE Confidence: 0.903299264285715

01:27:18.520 --> 01:27:20.655 We can see that this can be

NOTE Confidence: 0.903299264285715

01:27:20.655 --> 01:27:22.220 seen segregating in families,

NOTE Confidence: 0.903299264285715

01:27:22.220 --> 01:27:24.964 so maybe behaving a little bit more like

NOTE Confidence: 0.903299264285715

01:27:24.964 --> 01:27:28.104 a a monogenic disease, although again,

NOTE Confidence: 0.903299264285715

01:27:28.104 --> 01:27:31.478 it may not be a completely penetrant.

NOTE Confidence: 0.728367542

01:27:34.540 --> 01:27:36.540 Interestingly, I have two

NOTE Confidence: 0.728367542

01:27:36.540 --> 01:27:39.540 140 lies right next to PKD.

NOTE Confidence: 0.728367542

01:27:39.540 --> 01:27:43.353 One just a half a mega base away from P-81.

NOTE Confidence: 0.728367542

01:27:43.353 --> 01:27:47.137 So some variants in PKD one like this

NOTE Confidence: 0.728367542

01:27:47.137 --> 01:27:50.214 atypical splicing change here are also

NOTE Confidence: 0.728367542

01:27:50.214 --> 01:27:54.270 found to set Co segregate within families.

NOTE Confidence: 0.728367542

01:27:54.270 --> 01:27:57.150 With the with the IT 140 there and

NOTE Confidence: 0.728367542

01:27:57.150 --> 01:28:01.307 so it could be that in in some cases

NOTE Confidence: 0.728367542

01:28:01.307 --> 01:28:04.099 they're also modifying the phenotype.

NOTE Confidence: 0.728367542

01:28:04.100 --> 01:28:06.330 I think sometimes get families

NOTE Confidence: 0.728367542

01:28:06.330 --> 01:28:09.210 have been linked to pick anyone,

NOTE Confidence: 0.728367542

01:28:09.210 --> 01:28:11.740 and missense variants have been

NOTE Confidence: 0.728367542

01:28:11.740 --> 01:28:14.270 assigned as a pathogenic variant,

NOTE Confidence: 0.728367542

01:28:14.270 --> 01:28:16.808 but I think it's worth reconsidering

NOTE Confidence: 0.728367542

01:28:16.808 --> 01:28:19.758 them now and and maybe some of

NOTE Confidence: 0.728367542

01:28:19.758 --> 01:28:22.495 these are really I FT 140 families.

NOTE Confidence: 0.900705768

01:28:25.800 --> 01:28:28.190 If we look at the.

NOTE Confidence: 0.900705768

01:28:28.190 --> 01:28:30.176 Between the type and these families

NOTE Confidence: 0.900705768

01:28:30.176 --> 01:28:32.447 and see that they also have

NOTE Confidence: 0.900705768

01:28:32.447 --> 01:28:34.199 rather preserved renal function.

NOTE Confidence: 0.900705768

01:28:34.200 --> 01:28:36.783 Only one of the patients that we

NOTE Confidence: 0.900705768

01:28:36.783 --> 01:28:39.897 looked at had end stage renal disease,

NOTE Confidence: 0.900705768

01:28:39.900 --> 01:28:42.476 and they'd already had a a kidney

NOTE Confidence: 0.900705768

01:28:42.476 --> 01:28:45.624 removed at an early age because they had

NOTE Confidence: 0.900705768

01:28:45.624 --> 01:28:48.084 a Wilms tumor and we can see that the

NOTE Confidence: 0.900705768

01:28:48.084 --> 01:28:49.989 size of the kidneys is quite large here.

NOTE Confidence: 0.900705768

01:28:49.990 --> 01:28:55.246 Because of these few but very large cysts,

NOTE Confidence: 0.900705768

01:28:55.250 --> 01:28:59.340 so many of these will be given the kind of.

NOTE Confidence: 0.900705768

01:28:59.340 --> 01:29:01.336 A typical presentation defined

NOTE Confidence: 0.900705768

01:29:01.336 --> 01:29:04.330 by the by the imaging class.

NOTE Confidence: 0.717122321333333

01:29:07.250 --> 01:29:10.682 If again, we look at the

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NOTE Confidence: 0.717122321333333

01:29:10.682 --> 01:29:14.080 UK Biobank for IT140.

NOTE Confidence: 0.717122321333333

01:29:14.080 --> 01:29:16.534 We can see that there's an

NOTE Confidence: 0.717122321333333

01:29:16.534 --> 01:29:18.170 enrichment of pathogenic variance

NOTE Confidence: 0.717122321333333

01:29:18.243 --> 01:29:19.812 in IFTTT 140 that's significant,

NOTE Confidence: 0.717122321333333

01:29:19.812 --> 01:29:22.540 so pick any one pick any two

NOTE Confidence: 0.717122321333333

01:29:22.540 --> 01:29:24.560 obviously are significantly found,

NOTE Confidence: 0.717122321333333

01:29:24.560 --> 01:29:26.750 and this is looking at the

NOTE Confidence: 0.717122321333333

01:29:26.750 --> 01:29:27.845 cystic kidney phenotype.

NOTE Confidence: 0.717122321333333

01:29:27.850 --> 01:29:30.640 There was about 1400 patients

NOTE Confidence: 0.717122321333333

01:29:30.640 --> 01:29:33.430 within this population that were

NOTE Confidence: 0.717122321333333

01:29:33.526 --> 01:29:36.676 defined as having a cystic kidneys,

NOTE Confidence: 0.717122321333333

01:29:36.680 --> 01:29:38.750 and I have two 140 was found to be

NOTE Confidence: 0.717122321333333

01:29:38.750 --> 01:29:41.073 there at the third most common variant

NOTE Confidence: 0.717122321333333

01:29:41.073 --> 01:29:42.780 associated with that being done,

NOTE Confidence: 0.717122321333333

01:29:42.780 --> 01:29:44.364 and the only one the other

NOTE Confidence: 0.717122321333333

01:29:44.364 --> 01:29:45.420 one that was significant.

NOTE Confidence: 0.717122321333333

01:29:45.420 --> 01:29:46.830 You can see I have G9.

NOTE Confidence: 0.717122321333333

01:29:46.830 --> 01:29:50.592 There is one other that was seen but

NOTE Confidence: 0.717122321333333

01:29:50.592 --> 01:29:54.169 but not at a a significant level.

NOTE Confidence: 0.717122321333333

01:29:54.170 --> 01:29:58.356 And then again if we look at.

NOTE Confidence: 0.717122321333333

01:29:58.360 --> 01:29:59.728 High impact variance,

NOTE Confidence: 0.717122321333333

01:29:59.728 --> 01:30:02.920 so variants that are likely to be

NOTE Confidence: 0.717122321333333

01:30:03.006 --> 01:30:05.450 pathogenic in activating variants

NOTE Confidence: 0.717122321333333

01:30:05.450 --> 01:30:08.690 compared to synonymous or intronic variants.

NOTE Confidence: 0.717122321333333

01:30:08.690 --> 01:30:11.455 We can see there's a Richmond here

NOTE Confidence: 0.717122321333333

01:30:11.455 --> 01:30:14.570 in the cystic kidneys different two

NOTE Confidence: 0.717122321333333

01:30:14.570 --> 01:30:17.215 different defined cystic kidney phenotype.

NOTE Confidence: 0.717122321333333

01:30:17.220 --> 01:30:17.786 Interestingly,

NOTE Confidence: 0.717122321333333

01:30:17.786 --> 01:30:20.616 also in the CKD stage.

NOTE Confidence: 0.717122321333333

01:30:20.620 --> 01:30:22.264 4-5 although we didn't see renal

NOTE Confidence: 0.717122321333333

01:30:22.264 --> 01:30:24.120 failure in most of the patients,

NOTE Confidence: 0.717122321333333

01:30:24.120 --> 01:30:28.600 so we looked at but not other forms of.

NOTE Confidence: 0.717122321333333

01:30:28.600 --> 01:30:29.740 Kidney disease,

NOTE Confidence: 0.717122321333333

01:30:29.740 --> 01:30:32.590 again suggesting that there's a

NOTE Confidence: 0.717122321333333

01:30:32.590 --> 01:30:34.381 significant enrichment between

NOTE Confidence: 0.717122321333333

01:30:34.381 --> 01:30:37.221 pathogenic variants in this gene

NOTE Confidence: 0.717122321333333

01:30:37.221 --> 01:30:42.480 and PKD and the PKD phenotype.

NOTE Confidence: 0.717122321333333

01:30:42.480 --> 01:30:45.224 So I just want to follow up finish

NOTE Confidence: 0.717122321333333

01:30:45.224 --> 01:30:48.285 up by just talking about a couple

NOTE Confidence: 0.717122321333333

01:30:48.285 --> 01:30:51.120 of other dominant or mono allelic

NOTE Confidence: 0.717122321333333

01:30:51.120 --> 01:30:53.120 diseases that are associated

NOTE Confidence: 0.717122321333333

01:30:53.120 --> 01:30:56.085 with the NADPKD like phenotype

NOTE Confidence: 0.717122321333333

01:30:56.085 --> 01:30:59.360 so or facial digital one.

NOTE Confidence: 0.717122321333333

01:30:59.360 --> 01:31:01.658 This is an X linked dominant

NOTE Confidence: 0.717122321333333

01:31:01.658 --> 01:31:04.090 disease so we see this phenotype

NOTE Confidence: 0.717122321333333

01:31:04.090 --> 01:31:06.946 in in females where we just have

NOTE Confidence: 0.717122321333333

01:31:06.946 --> 01:31:09.520 a single pathogenic allele.

NOTE Confidence: 0.717122321333333

01:31:09.520 --> 01:31:12.817 They also have a variety of facial.

NOTE Confidence: 0.717122321333333

01:31:12.820 --> 01:31:15.915 World Digital and and central

NOTE Confidence: 0.717122321333333

01:31:15.915 --> 01:31:18.391 nervous system phenotype associated

NOTE Confidence: 0.717122321333333

01:31:18.391 --> 01:31:21.557 as well as the cystic kidneys,

NOTE Confidence: 0.717122321333333

01:31:21.560 --> 01:31:24.500 but it's sometimes we can see

NOTE Confidence: 0.717122321333333

01:31:24.500 --> 01:31:27.019 cystic kidney phenotype and and

NOTE Confidence: 0.717122321333333

01:31:27.019 --> 01:31:29.379 only mild other phenotypes and

NOTE Confidence: 0.717122321333333

01:31:29.379 --> 01:31:32.810 they can be mistaken for a DPKD.

NOTE Confidence: 0.945061954

01:31:35.100 --> 01:31:39.920 Recently we've been looking at

NOTE Confidence: 0.945061954

01:31:39.920 --> 01:31:41.804 specific variants in NEKADE.

NOTE Confidence: 0.945061954

01:31:41.804 --> 01:31:45.697 This is a a kinase that is thought

NOTE Confidence: 0.945061954

01:31:45.697 --> 01:31:48.619 to be associated with the cilia.

NOTE Confidence: 0.945061954

01:31:48.620 --> 01:31:50.540 This is following up with an

NOTE Confidence: 0.945061954

01:31:50.540 --> 01:31:52.580 abstract that was published last

NOTE Confidence: 0.945061954

01:31:52.580 --> 01:31:55.280 year or presented last year.

NOTE Confidence: 0.945061954

01:31:55.280 --> 01:31:58.868 The SN and in these cases

NOTE Confidence: 0.945061954

01:31:58.868 --> 01:32:01.730 the disease is associated so.

NOTE Confidence: 0.682606581125

01:32:03.810 --> 01:32:06.972 Bylica Neck 8 variants are again

NOTE Confidence: 0.682606581125

01:32:06.972 --> 01:32:09.875 associated with a a ciliopathy

NOTE Confidence: 0.682606581125

01:32:09.875 --> 01:32:13.335 type phenotype and where some.

NOTE Confidence: 0.682606581125

01:32:13.340 --> 01:32:17.159 Animal models are nice models JCK

NOTE Confidence: 0.682606581125

01:32:17.159 --> 01:32:20.153 that are associated with neck height

NOTE Confidence: 0.682606581125

01:32:20.153 --> 01:32:23.199 variance or in a recessive way.

NOTE Confidence: 0.682606581125

01:32:23.200 --> 01:32:27.412 But here we have a just a single allele.

NOTE Confidence: 0.682606581125

01:32:27.420 --> 01:32:29.975 This is associated with very severe disease.

NOTE Confidence: 0.682606581125

01:32:29.980 --> 01:32:32.436 You can see end stage renal disease at

NOTE Confidence: 0.682606581125

01:32:32.436 --> 01:32:35.267 one year of age here in the in the mother,

NOTE Confidence: 0.682606581125

01:32:35.270 --> 01:32:37.986 but other she had the three transplants

NOTE Confidence: 0.682606581125

01:32:37.986 --> 01:32:41.108 and was able to give rise to a child

NOTE Confidence: 0.682606581125

01:32:41.108 --> 01:32:43.339 that also had this very severe.

NOTE Confidence: 0.682606581125

01:32:43.340 --> 01:32:45.290 Disease here you can see the

NOTE Confidence: 0.682606581125

01:32:45.290 --> 01:32:47.374 light and large cystic kidneys.

NOTE Confidence: 0.682606581125

01:32:47.374 --> 01:32:50.686 OK in large cystic kidneys here,

NOTE Confidence: 0.682606581125

01:32:50.690 --> 01:32:51.965 although interestingly made

NOTE Confidence: 0.682606581125

01:32:51.965 --> 01:32:54.090 up of rather larger cysts,

NOTE Confidence: 0.682606581125

01:32:54.090 --> 01:32:57.924 and we typically see in the in the RPD.

NOTE Confidence: 0.682606581125

01:32:57.930 --> 01:32:58.271 Interestingly,

NOTE Confidence: 0.682606581125

01:32:58.271 --> 01:33:00.658 the mother had end stage of 48

NOTE Confidence: 0.682606581125

01:33:00.658 --> 01:33:03.230 years of age of the consider the

NOTE Confidence: 0.682606581125

01:33:03.230 --> 01:33:04.690 kidneys look fairly similar,

NOTE Confidence: 0.682606581125

01:33:04.690 --> 01:33:07.338 and she was only a mosaic for the

NOTE Confidence: 0.682606581125

01:33:07.338 --> 01:33:10.321 for the variant here you can see the

NOTE Confidence: 0.682606581125

01:33:10.321 --> 01:33:13.349 the the the level of the the mutant.

NOTE Confidence: 0.682606581125

01:33:13.350 --> 01:33:15.090 There was very low,

NOTE Confidence: 0.682606581125

01:33:15.090 --> 01:33:19.220 so that's why she had much milder disease.

NOTE Confidence: 0.682606581125

01:33:19.220 --> 01:33:20.980 And this is second family.

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NOTE Confidence: 0.682606581125

01:33:20.980 --> 01:33:24.652 Here you can see that the these very

NOTE Confidence: 0.682606581125

01:33:24.652 --> 01:33:27.360 large cystic kidneys here where

NOTE Confidence: 0.682606581125

01:33:27.360 --> 01:33:29.364 birds started at seven years of

NOTE Confidence: 0.682606581125

01:33:29.364 --> 01:33:31.779 age from from this parent patient.

NOTE Confidence: 0.682606581125

01:33:31.780 --> 01:33:34.078 So the difference between the variance

NOTE Confidence: 0.682606581125

01:33:34.078 --> 01:33:37.329 here and in neck 8 compared to the

NOTE Confidence: 0.682606581125

01:33:37.329 --> 01:33:39.384 recessive diseases of these variants

NOTE Confidence: 0.682606581125

01:33:39.384 --> 01:33:42.237 seem to be in the in the kinase domain,

NOTE Confidence: 0.682606581125

01:33:42.240 --> 01:33:44.592 so they're having a much more

NOTE Confidence: 0.682606581125

01:33:44.592 --> 01:33:47.230 severe form of the the disease.

NOTE Confidence: 0.715550862166667

01:33:49.730 --> 01:33:54.420 And just finally we can see also

NOTE Confidence: 0.715550862166667

01:33:54.420 --> 01:33:56.430 synergy synergistic interactions

NOTE Confidence: 0.715550862166667

01:33:56.536 --> 01:33:59.690 between the P-81 and the pH one.

NOTE Confidence: 0.715550862166667

01:33:59.690 --> 01:34:03.246 So the gene associated with AARP KD

NOTE Confidence: 0.715550862166667

01:34:03.246 --> 01:34:07.136 that Steve is described and we've

NOTE Confidence: 0.715550862166667

01:34:07.136 --> 01:34:09.804 confirmed this is looking at a a

NOTE Confidence: 0.715550862166667

01:34:09.804 --> 01:34:13.455 rat model of ARP KD that it has this

NOTE Confidence: 0.715550862166667

01:34:13.455 --> 01:34:15.745 slowly progressive disease PCK wrap.

NOTE Confidence: 0.715550862166667

01:34:15.750 --> 01:34:19.607 We made a a heterozygous P-81.

NOTE Confidence: 0.715550862166667

01:34:19.607 --> 01:34:22.589 Knockout a Leo which by itself

NOTE Confidence: 0.715550862166667

01:34:22.589 --> 01:34:25.909 has very few cysts developing.

NOTE Confidence: 0.715550862166667

01:34:25.910 --> 01:34:28.900 But then if we can see the the

NOTE Confidence: 0.715550862166667

01:34:28.900 --> 01:34:31.870 them together we have this much

NOTE Confidence: 0.715550862166667

01:34:31.870 --> 01:34:34.760 more severe synergistic phenotype,

NOTE Confidence: 0.715550862166667

01:34:34.760 --> 01:34:38.410 indicating that that the ARP,

NOTE Confidence: 0.715550862166667

01:34:38.410 --> 01:34:40.470 KD and AD PKD proteins.

NOTE Confidence: 0.715550862166667

01:34:40.470 --> 01:34:42.490 Although we don't think they

NOTE Confidence: 0.715550862166667

01:34:42.490 --> 01:34:44.510 interact and form a complex,

NOTE Confidence: 0.715550862166667

01:34:44.510 --> 01:34:47.924 have some type of related role

NOTE Confidence: 0.715550862166667

01:34:47.924 --> 01:34:50.200 in preventing system development.

NOTE Confidence: 0.715550862166667

01:34:50.200 --> 01:34:51.811 Within the kidney.

NOTE Confidence: 0.715550862166667

01:34:51.811 --> 01:34:52.348 Interesting,

NOTE Confidence: 0.715550862166667

01:34:52.348 --> 01:34:57.549 we did some RNA seek and in the in the

NOTE Confidence: 0.715550862166667

01:34:57.549 --> 01:35:00.369 three populations here the the the.

NOTE Confidence: 0.715550862166667

01:35:00.370 --> 01:35:03.382 The Geo terms that were all

NOTE Confidence: 0.715550862166667

01:35:03.382 --> 01:35:05.390 associated with cilia development.

NOTE Confidence: 0.715550862166667

01:35:05.390 --> 01:35:08.911 We also saw a longer cilia here

NOTE Confidence: 0.715550862166667

01:35:08.911 --> 01:35:11.874 in these diegetic animals than we

NOTE Confidence: 0.715550862166667

01:35:11.874 --> 01:35:13.746 saw in the the normal individual.

NOTE Confidence: 0.715550862166667

01:35:13.750 --> 01:35:17.002 So whether this is directly associated

NOTE Confidence: 0.715550862166667

01:35:17.002 --> 01:35:20.405 with these these mutations or is a

NOTE Confidence: 0.715550862166667

01:35:20.405 --> 01:35:23.770 response to lack of cilia signaling,

NOTE Confidence: 0.715550862166667

01:35:23.770 --> 01:35:27.347 I think is a is a question.

NOTE Confidence: 0.715550862166667

01:35:27.350 --> 01:35:29.910 So we can see as well as the

NOTE Confidence: 0.715550862166667

01:35:29.910 --> 01:35:33.546 variance associated with the folding

NOTE Confidence: 0.715550862166667

01:35:33.546 --> 01:35:34.778 of police system one,

NOTE Confidence: 0.715550862166667

01:35:34.780 --> 01:35:37.370 giving rise to an 80 P80 phenotype.

NOTE Confidence: 0.715550862166667

01:35:37.370 --> 01:35:39.911 We can see variance as well as

NOTE Confidence: 0.715550862166667

01:35:39.911 --> 01:35:42.723 the Piketty one and Piketty 2 and

NOTE Confidence: 0.715550862166667

01:35:42.723 --> 01:35:45.183 and five persistent on the cilium.

NOTE Confidence: 0.715550862166667

01:35:45.190 --> 01:35:48.436 We can see these other variants

NOTE Confidence: 0.715550862166667

01:35:48.436 --> 01:35:50.600 associated with different parts

NOTE Confidence: 0.715550862166667

01:35:50.686 --> 01:35:53.391 of which are associated with

NOTE Confidence: 0.715550862166667

01:35:53.391 --> 01:35:56.440 ciliopathies and are recessive way or.

NOTE Confidence: 0.559430941666667

01:35:58.840 --> 01:36:02.416 The X linked OFT one here,

NOTE Confidence: 0.559430941666667

01:36:02.420 --> 01:36:04.580 resulting in in something

NOTE Confidence: 0.559430941666667

01:36:04.580 --> 01:36:07.280 like an ad PKD phenotype.

NOTE Confidence: 0.559430941666667

01:36:07.280 --> 01:36:09.058 So I think the question is here,

NOTE Confidence: 0.559430941666667

01:36:09.060 --> 01:36:11.751 are these working and you can see that they

NOTE Confidence: 0.559430941666667

01:36:11.751 --> 01:36:14.236 seem to be in different complexes here,

NOTE Confidence: 0.559430941666667

01:36:14.240 --> 01:36:18.560 but may all all all be associated with.

NOTE Confidence: 0.559430941666667

01:36:18.560 --> 01:36:20.380 Determining the level of power

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NOTE Confidence: 0.559430941666667

01:36:20.380 --> 01:36:22.613 system one policy system 2 maybe

NOTE Confidence: 0.559430941666667

01:36:22.613 --> 01:36:24.318 fibre system on the cilia.

NOTE Confidence: 0.559430941666667

01:36:24.320 --> 01:36:28.208 So is this a mechanism of disease or

NOTE Confidence: 0.559430941666667

01:36:28.208 --> 01:36:32.169 is there other cilia related cisgenic

NOTE Confidence: 0.559430941666667

01:36:32.169 --> 01:36:35.666 pathways as Steve's work has suggested

NOTE Confidence: 0.559430941666667

01:36:35.666 --> 01:36:39.632 that might be in important in the in

NOTE Confidence: 0.559430941666667

01:36:39.632 --> 01:36:43.216 the in the formation of this disease.

NOTE Confidence: 0.559430941666667

01:36:43.220 --> 01:36:47.725 So I just to summarize P-81 and Piketty

NOTE Confidence: 0.559430941666667

01:36:47.725 --> 01:36:52.318 2 are the the the common 80 PKD genes.

NOTE Confidence: 0.559430941666667

01:36:52.320 --> 01:36:54.480 P-81 is more severe than P82.

NOTE Confidence: 0.559430941666667

01:36:54.480 --> 01:36:57.340 Truncating and more severe

NOTE Confidence: 0.559430941666667

01:36:57.340 --> 01:36:59.485 than non truncating.

NOTE Confidence: 0.559430941666667

01:36:59.490 --> 01:37:02.265 There we see genetic complexity

NOTE Confidence: 0.559430941666667

01:37:02.265 --> 01:37:03.930 of biallelic disease,

NOTE Confidence: 0.559430941666667

01:37:03.930 --> 01:37:05.382 complex alleles,

NOTE Confidence: 0.559430941666667

01:37:05.382 --> 01:37:08.286 mosaicism and digenic disease,

NOTE Confidence: 0.559430941666667

01:37:08.290 --> 01:37:11.055 a dosage model we feel fits the

NOTE Confidence: 0.559430941666667

01:37:11.055 --> 01:37:13.708 the data we see in terms of

NOTE Confidence: 0.559430941666667

01:37:13.710 --> 01:37:16.140 the genetic mechanism in in 80,

NOTE Confidence: 0.559430941666667

01:37:16.140 --> 01:37:17.334 PKD monogenic,

NOTE Confidence: 0.559430941666667

01:37:17.334 --> 01:37:20.319 pathogenic variance in ER proteins

NOTE Confidence: 0.559430941666667

01:37:20.319 --> 01:37:23.416 that involved in these different

NOTE Confidence: 0.559430941666667

01:37:23.416 --> 01:37:27.052 processes for dealing with a membrane

NOTE Confidence: 0.559430941666667

01:37:27.052 --> 01:37:30.348 and truncated and secreted proteins.

NOTE Confidence: 0.559430941666667

01:37:30.350 --> 01:37:31.930 Are associated with an ADP,

NOTE Confidence: 0.559430941666667

01:37:31.930 --> 01:37:35.866 KD or 80 PLD phenotype and maybe associated

NOTE Confidence: 0.559430941666667

01:37:35.866 --> 01:37:38.948 with Polar system one maturation.

NOTE Confidence: 0.559430941666667

01:37:38.950 --> 01:37:42.022 Now we're seeing increasing number of

NOTE Confidence: 0.559430941666667

01:37:42.022 --> 01:37:44.900 variants associated with cilia structure.

NOTE Confidence: 0.559430941666667

01:37:44.900 --> 01:37:48.330 Also associated with a ADP.

NOTE Confidence: 0.559430941666667

01:37:48.330 --> 01:37:50.526 KD like phenotype and and is

NOTE Confidence: 0.559430941666667

01:37:50.526 --> 01:37:53.333 this to do with the level of

NOTE Confidence: 0.559430941666667

01:37:53.333 --> 01:37:56.639 ciliary power system one.

NOTE Confidence: 0.559430941666667

01:37:56.640 --> 01:37:59.016 So you just want to thank the the

NOTE Confidence: 0.559430941666667

01:37:59.016 --> 01:38:01.266 people in my lab over the last decade

NOTE Confidence: 0.559430941666667

01:38:01.266 --> 01:38:03.152 that have been involved with the

NOTE Confidence: 0.559430941666667

01:38:03.152 --> 01:38:05.448 the works that we've been doing and

NOTE Confidence: 0.559430941666667

01:38:05.512 --> 01:38:08.620 also John Sayer and Eric Hollinger

NOTE Confidence: 0.559430941666667

01:38:08.620 --> 01:38:11.480 in Newcastle for the collaborations

NOTE Confidence: 0.559430941666667

01:38:11.572 --> 01:38:14.675 on the the work associated with the

NOTE Confidence: 0.559430941666667

01:38:14.675 --> 01:38:18.168 UK Biobank and the 100,000 genome project.

NOTE Confidence: 0.559430941666667

01:38:18.168 --> 01:38:19.120 Thank you.

NOTE Confidence: 0.434000395

01:38:40.100 --> 01:38:40.830 Showing that.

NOTE Confidence: 0.66171044

01:38:47.380 --> 01:38:50.220 Right? Those are one of the beach.

NOTE Confidence: 0.0809772

01:38:55.760 --> 01:38:56.490 Yeah.

NOTE Confidence: 0.782775972

01:39:05.060 --> 01:39:06.792 Yeah, I don't know.

NOTE Confidence: 0.782775972

01:39:06.792 --> 01:39:10.342 I guess in in our hands we also

NOTE Confidence: 0.782775972

01:39:10.342 --> 01:39:13.198 find that to be a trafficking

NOTE Confidence: 0.782775972

01:39:13.198 --> 01:39:16.439 mutation and we find less of that or

NOTE Confidence: 0.782775972

01:39:16.440 --> 01:39:18.160 that it doesn't traffic properly.

NOTE Confidence: 0.782775972

01:39:18.160 --> 01:39:22.740 So yeah, I I'm I'm not sure about that.

NOTE Confidence: 0.782775972

01:39:22.740 --> 01:39:24.927 I think it depends a little bit on the

NOTE Confidence: 0.782775972

01:39:24.927 --> 01:39:26.859 system that you're that you're using,

NOTE Confidence: 0.782775972

01:39:26.860 --> 01:39:27.680 but certainly.

NOTE Confidence: 0.782775972

01:39:27.680 --> 01:39:31.692 We've also found that to be a trafficking

NOTE Confidence: 0.782775972

01:39:31.692 --> 01:39:36.405 defect and and so I don't know exactly

NOTE Confidence: 0.782775972

01:39:36.405 --> 01:39:39.280 how to to reconcile that data.

NOTE Confidence: 0.12792012

01:39:41.510 --> 01:39:42.080 Pardon.

NOTE Confidence: 0.92989286

01:39:44.220 --> 01:39:46.100 Right, right exactly yeah, yeah.

NOTE Confidence: 0.92989286

01:39:46.100 --> 01:39:50.008 So overexpressed tag protein.

NOTE Confidence: 0.92989286

01:39:50.010 --> 01:39:52.338 Pressing policy system one and police

NOTE Confidence: 0.92989286

01:39:52.338 --> 01:39:55.170 system two and we're looking at salary.

NOTE Confidence: 0.92989286

01:39:55.170 --> 01:39:56.930 You know, surface localization here,

NOTE Confidence: 0.92989286

01:39:56.930 --> 01:39:58.157 not ciliary localization.

NOTE Confidence: 0.92989286

01:39:58.157 --> 01:40:01.020 And there could be a different layer.

NOTE Confidence: 0.92989286

01:40:01.020 --> 01:40:03.282 Reviews the surface as a kind

NOTE Confidence: 0.92989286

01:40:03.282 --> 01:40:05.320 of surrogate for the cilia,

NOTE Confidence: 0.92989286

01:40:05.320 --> 01:40:07.108 but you know it may not

NOTE Confidence: 0.92989286

01:40:07.108 --> 01:40:08.890 be a complete one to one.

NOTE Confidence: 0.896562625

01:40:12.010 --> 01:40:13.110 Similarity there.

NOTE Confidence: 0.7223654

01:40:17.490 --> 01:40:21.138 So the energy is staggering.

NOTE Confidence: 0.556283

01:40:27.650 --> 01:40:28.900 We're able to develop there.

NOTE Confidence: 0.19094557

01:40:33.930 --> 01:40:34.360 Interesting.

NOTE Confidence: 0.821957936842105

01:40:50.660 --> 01:40:53.096 Yeah, I think it's a time where

NOTE Confidence: 0.821957936842105

01:40:53.096 --> 01:40:55.621 we can start thinking about more

NOTE Confidence: 0.821957936842105

01:40:55.621 --> 01:40:58.417 tailored therapies for for a PKD.

NOTE Confidence: 0.821957936842105

01:40:58.420 --> 01:41:01.132 As I mentioned, chaperones might be

NOTE Confidence: 0.821957936842105

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01:41:01.132 --> 01:41:04.419 useful for for some missense changes.

NOTE Confidence: 0.821957936842105

01:41:04.420 --> 01:41:06.240 We've been looking at nonsense.

NOTE Confidence: 0.821957936842105

01:41:06.240 --> 01:41:09.318 We through as a as a possibility where you

NOTE Confidence: 0.821957936842105

01:41:09.318 --> 01:41:12.654 know a quarter of patients would pick anyone,

NOTE Confidence: 0.821957936842105

01:41:12.660 --> 01:41:15.971 have nonsense mutations and the and the

NOTE Confidence: 0.821957936842105

01:41:15.971 --> 01:41:19.119 read through of functional protein.

NOTE Confidence: 0.821957936842105

01:41:19.120 --> 01:41:20.480 Maybe helpful, you know.

NOTE Confidence: 0.821957936842105

01:41:20.480 --> 01:41:22.879 And this sort of dosage model is

NOTE Confidence: 0.821957936842105

01:41:22.879 --> 01:41:24.655 is making us think about that.

NOTE Confidence: 0.821957936842105

01:41:24.660 --> 01:41:28.296 Even if we could increase the level by 10%,

NOTE Confidence: 0.821957936842105

01:41:28.296 --> 01:41:31.602 that may be a significant effect.

NOTE Confidence: 0.821957936842105

01:41:31.602 --> 01:41:33.922 I think Steve's work where

NOTE Confidence: 0.821957936842105

01:41:33.922 --> 01:41:36.488 you know you can re express.

NOTE Confidence: 0.821957936842105

01:41:36.490 --> 01:41:39.416 Polar systems and and rescue the phenotype

NOTE Confidence: 0.821957936842105

01:41:39.416 --> 01:41:42.427 is also very exciting in that area,

NOTE Confidence: 0.821957936842105

01:41:42.430 --> 01:41:45.964 suggesting that these types of are,

01:41:45.964 --> 01:41:46.672 you know,

01:41:46.672 --> 01:41:48.796 increasing the level of police system

01:41:48.796 --> 01:41:50.922 and obviously you know going in

01:41:50.922 --> 01:41:53.070 with crisper and trying to repair

01:41:53.070 --> 01:41:55.681 the the variant or maybe using a

01:41:55.681 --> 01:41:58.455 transgenic approach and and re

01:41:58.455 --> 01:42:01.830 expressing the protein or Michael.

01:42:01.830 --> 01:42:05.156 Things might be work just to re

01:42:05.156 --> 01:42:07.764 express the the part of the sea tail.

01:42:07.770 --> 01:42:11.893 I think all of these are exciting

01:42:11.893 --> 01:42:14.715 possible therapies and some of

01:42:14.715 --> 01:42:17.198 them you know would we would.

01:42:17.198 --> 01:42:19.256 We would want to know the genotype

01:42:19.256 --> 01:42:21.464 of the of the patient and some

01:42:21.464 --> 01:42:23.450 may be more generally applicable.

01:42:23.450 --> 01:42:24.502 But I think so.

NOTE Confidence: 0.821957936842105

01:42:24.502 --> 01:42:25.028 I mean,

NOTE Confidence: 0.821957936842105

01:42:25.030 --> 01:42:26.962 I think that you know targeting

NOTE Confidence: 0.821957936842105

01:42:26.962 --> 01:42:27.928 the downstream pathways.

NOTE Confidence: 0.821957936842105

01:42:27.930 --> 01:42:29.658 Although we have a therapy right

NOTE Confidence: 0.821957936842105

01:42:29.658 --> 01:42:31.449 now that works to an extent.

NOTE Confidence: 0.821957936842105

01:42:31.450 --> 01:42:34.600 I think it's not a cure for for any big D,

NOTE Confidence: 0.821957936842105

01:42:34.600 --> 01:42:36.706 and I think looking more approximately

NOTE Confidence: 0.821957936842105

01:42:36.706 --> 01:42:39.215 in the pathway and trying to correct

NOTE Confidence: 0.821957936842105

01:42:39.215 --> 01:42:40.940 the basic defect is something

NOTE Confidence: 0.821957936842105

01:42:40.940 --> 01:42:43.177 that the the field should really

NOTE Confidence: 0.821957936842105

01:42:43.177 --> 01:42:45.027 be concentrating on right now.

NOTE Confidence: 0.587447086666667

01:43:00.670 --> 01:43:01.378 I know that.

NOTE Confidence: 0.933828293571428

01:43:31.030 --> 01:43:33.534 Yeah, I don't know if those two things

NOTE Confidence: 0.933828293571428

01:43:33.534 --> 01:43:36.067 are are associated with each other.

NOTE Confidence: 0.933828293571428

01:43:36.070 --> 01:43:37.735 I mean it. The association

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NOTE Confidence: 0.933828293571428

01:43:37.735 --> 01:43:40.489 may be to do with folding and

NOTE Confidence: 0.933828293571428

01:43:40.489 --> 01:43:42.509 and trafficking of proteins.

NOTE Confidence: 0.933828293571428

01:43:42.510 --> 01:43:46.438 I think in a more more general way

NOTE Confidence: 0.933828293571428

01:43:46.438 --> 01:43:49.331 so but I don't know of any other

NOTE Confidence: 0.933828293571428

01:43:49.331 --> 01:43:50.820 more direct association there.

NOTE Confidence: 0.641479343333333

01:43:53.000 --> 01:43:53.630 You're very nice.

NOTE Confidence: 0.5400234825

01:43:56.900 --> 01:43:57.948 For quite some time.

NOTE Confidence: 0.537279

01:44:01.010 --> 01:44:01.540 ER

NOTE Confidence: 0.16779616

01:44:07.770 --> 01:44:08.290 predominant.

NOTE Confidence: 0.569693466

01:44:11.860 --> 01:44:13.380 Step back from our colleague.

NOTE Confidence: 0.716998752

01:44:15.690 --> 01:44:16.820 I would imagine that many.

NOTE Confidence: 0.64433514

01:44:20.110 --> 01:44:20.740 More success.

NOTE Confidence: 0.78852565

01:44:24.030 --> 01:44:26.535 Thank you. Perceptor

NOTE Confidence: 0.78852565

01:44:26.535 --> 01:44:28.170 complex finance channels.

NOTE Confidence: 0.5401724

01:44:30.780 --> 01:44:34.338 That's. Has anyone looked at

NOTE Confidence: 0.5401724

01:44:34.338 --> 01:44:36.723 patients with either the polycystic

NOTE Confidence: 0.5401724

01:44:36.723 --> 01:44:39.242 liver or published kidney protein

NOTE Confidence: 0.5401724

01:44:39.242 --> 01:44:41.306 folding associated with patients

NOTE Confidence: 0.5401724

01:44:41.306 --> 01:44:44.090 to keep their phenotypic analysis?

NOTE Confidence: 0.5401724

01:44:44.090 --> 01:44:45.290 For example, T cell.

NOTE Confidence: 0.655201041181818

01:44:48.030 --> 01:44:49.470 Cardiac myocyte organization,

NOTE Confidence: 0.655201041181818

01:44:49.470 --> 01:44:52.830 etcetera etcetera to try and get a

NOTE Confidence: 0.655201041181818

01:44:52.914 --> 01:44:55.842 sense of this phenotype extension would

NOTE Confidence: 0.655201041181818

01:44:55.842 --> 01:44:58.699 broadly to other proteins that might.

NOTE Confidence: 0.655201041181818

01:44:58.700 --> 01:45:00.436 Yeah, I mean, I think you know

NOTE Confidence: 0.655201041181818

01:45:00.436 --> 01:45:01.619 we're certainly aware of that,

NOTE Confidence: 0.655201041181818

01:45:01.620 --> 01:45:03.748 and I think it is a little bit

NOTE Confidence: 0.655201041181818

01:45:03.748 --> 01:45:05.689 naive to say that these patients

NOTE Confidence: 0.655201041181818

01:45:05.689 --> 01:45:07.693 just have PKD or or PLMD.

NOTE Confidence: 0.655201041181818

01:45:07.700 --> 01:45:10.129 And you know, we've tried to look

NOTE Confidence: 0.655201041181818

01:45:10.129 --> 01:45:11.649 for other associated phenotypes

NOTE Confidence: 0.655201041181818

01:45:11.649 --> 01:45:13.704 in the relatively small number

NOTE Confidence: 0.655201041181818

01:45:13.704 --> 01:45:15.740 of patients that we've seen.

NOTE Confidence: 0.655201041181818

01:45:15.740 --> 01:45:17.850 And although there's some clues,

NOTE Confidence: 0.655201041181818

01:45:17.850 --> 01:45:21.339 sometimes nothing really.

NOTE Confidence: 0.655201041181818

01:45:21.340 --> 01:45:22.978 Something that we can be certain of,

NOTE Confidence: 0.655201041181818

01:45:22.980 --> 01:45:24.580 and I think that's to do with the

NOTE Confidence: 0.655201041181818

01:45:24.580 --> 01:45:26.197 number of small number of patients.

NOTE Confidence: 0.655201041181818

01:45:26.200 --> 01:45:28.370 I think the you know things like

NOTE Confidence: 0.655201041181818

01:45:28.370 --> 01:45:31.084 the UK Biobank and the you know 100

NOTE Confidence: 0.655201041181818

01:45:31.084 --> 01:45:33.232 genomes projects are really the places

NOTE Confidence: 0.655201041181818

01:45:33.232 --> 01:45:35.773 to look for these where there are

NOTE Confidence: 0.655201041181818

01:45:35.773 --> 01:45:38.640 especially for a LG eight you know

NOTE Confidence: 0.655201041181818

01:45:38.640 --> 01:45:41.474 larger number of of patients and ask

NOTE Confidence: 0.655201041181818

01:45:41.474 --> 01:45:43.209 questions about whether there's other

NOTE Confidence: 0.655201041181818

01:45:43.209 --> 01:45:44.540 phenotypes associated with that.

NOTE Confidence: 0.655201041181818

01:45:44.540 --> 01:45:46.745 I know that John and Eric have

NOTE Confidence: 0.655201041181818

01:45:46.745 --> 01:45:49.117 tried to do that a little bit.

NOTE Confidence: 0.655201041181818

01:45:49.120 --> 01:45:52.347 I don't think maybe there's a definitive.

NOTE Confidence: 0.655201041181818

01:45:52.350 --> 01:45:53.910 Word on on that yet,

NOTE Confidence: 0.655201041181818

01:45:53.910 --> 01:45:55.373 but I think that that is the

NOTE Confidence: 0.655201041181818

01:45:55.373 --> 01:45:57.280 way to to look at these and and.

NOTE Confidence: 0.655201041181818

01:45:57.280 --> 01:45:58.666 But I certainly agree with you.

NOTE Confidence: 0.655201041181818

01:45:58.670 --> 01:46:01.318 I think that you know just to say

NOTE Confidence: 0.655201041181818

01:46:01.318 --> 01:46:03.936 that these are a PKD or PLD disease.

NOTE Confidence: 0.655201041181818

01:46:03.940 --> 01:46:07.140 When there's a lightly a lot of other

NOTE Confidence: 0.655201041181818

01:46:07.140 --> 01:46:08.771 proteins associated is probably

NOTE Confidence: 0.655201041181818

01:46:08.771 --> 01:46:11.033 a bit naive and under estimate.

NOTE Confidence: 0.655201041181818

01:46:11.040 --> 01:46:13.056 And obviously you know these patients

NOTE Confidence: 0.655201041181818

01:46:13.056 --> 01:46:15.835 may be at risk for for other diseases

NOTE Confidence: 0.655201041181818

01:46:15.835 --> 01:46:18.669 that that we should be telling them about.

NOTE Confidence: 0.655201041181818

01:46:18.670 --> 01:46:20.752 If we could better understand what

NOTE Confidence: 0.655201041181818

01:46:20.752 --> 01:46:22.789 what might be associated with that.

NOTE Confidence: 0.5339132675

01:46:26.350 --> 01:46:27.978 Doctor Harris great talk

NOTE Confidence: 0.5825527

01:46:30.720 --> 01:46:31.090 OK.

NOTE Confidence: 0.778395369

01:46:34.300 --> 01:46:36.386 We'll reconvene in like 5 minutes for

NOTE Confidence: 0.778395369

01:46:36.386 --> 01:46:38.388 the next speaker, which will be virtual.

NOTE Confidence: 0.808424124615385

01:46:40.550 --> 01:46:43.483 All right, I think we'll reconvene our

NOTE Confidence: 0.808424124615385

01:46:43.483 --> 01:46:46.369 next speaker is Doctor Sylvia Rosas,

NOTE Confidence: 0.808424124615385

01:46:46.370 --> 01:46:49.412 who's going to be from Harbor

NOTE Confidence: 0.808424124615385

01:46:49.412 --> 01:46:52.414 Medical School and discussing non

NOTE Confidence: 0.808424124615385

01:46:52.414 --> 01:46:55.060 steroidal mineralocorticoid receptor.

NOTE Confidence: 0.808424124615385

01:46:55.060 --> 01:46:56.440 Antagonists and individuals

NOTE Confidence: 0.808424124615385

01:46:56.440 --> 01:46:59.200 with CKD and Type 2 diabetes.

NOTE Confidence: 0.936921758

01:47:03.530 --> 01:47:05.890 Great, thank you very much.

NOTE Confidence: 0.936921758

01:47:05.890 --> 01:47:08.428 I hope everybody can hear me and see me.

NOTE Confidence: 0.936921758

01:47:08.430 --> 01:47:10.548 If not, please let me know.

NOTE Confidence: 0.936921758

01:47:10.550 --> 01:47:13.970 And so it is a great honor to be

NOTE Confidence: 0.936921758

01:47:13.970 --> 01:47:16.669 speaking today in this symposium,

NOTE Confidence: 0.936921758

01:47:16.670 --> 01:47:18.952 and I want to thank the organizers

NOTE Confidence: 0.936921758

01:47:18.952 --> 01:47:20.776 for inviting me and I hope

NOTE Confidence: 0.936921758

01:47:20.776 --> 01:47:22.750 that at the end of this talk,

NOTE Confidence: 0.936921758

01:47:22.750 --> 01:47:24.322 you'll agree with me that it's

NOTE Confidence: 0.936921758

01:47:24.322 --> 01:47:25.950 a great time to be doing.

NOTE Confidence: 0.936921758

01:47:25.950 --> 01:47:27.414 Being in a prologistix,

NOTE Confidence: 0.936921758

01:47:27.414 --> 01:47:30.023 and it's a great time to be

NOTE Confidence: 0.936921758

01:47:30.023 --> 01:47:32.045 in the Type 2 diabetes area.

NOTE Confidence: 0.936921758

01:47:32.050 --> 01:47:34.992 So these are my disclosures I guess

NOTE Confidence: 0.936921758

01:47:34.992 --> 01:47:37.218 for this talk the most important

NOTE Confidence: 0.936921758

01:47:37.218 --> 01:47:39.319 disclosure is that I participated

NOTE Confidence: 0.936921758

01:47:39.319 --> 01:47:41.464 in the Figuran Fidelio trials,

NOTE Confidence: 0.936921758

01:47:41.470 --> 01:47:44.968 and I'm a fidelity investigator too,

NOTE Confidence: 0.936921758

01:47:44.970 --> 01:47:47.686 so I think those are the most

NOTE Confidence: 0.936921758

01:47:47.686 --> 01:47:49.291 important for this presentation.

NOTE Confidence: 0.936921758

01:47:49.291 --> 01:47:49.732 Initially,

NOTE Confidence: 0.936921758

01:47:49.732 --> 01:47:53.260 I'll do a quick overview of the standard

NOTE Confidence: 0.936921758

01:47:53.335 --> 01:47:55.850 treatment of diabetic kidney disease,

NOTE Confidence: 0.936921758

01:47:55.850 --> 01:47:58.776 but I'm really going to focus on some

NOTE Confidence: 0.936921758

01:47:58.776 --> 01:48:01.338 work that we've done using the combined

NOTE Confidence: 0.936921758

01:48:01.338 --> 01:48:03.938 data set of the figure and Fidelio.

NOTE Confidence: 0.936921758

01:48:03.940 --> 01:48:07.612 Trials and at the end I'm going to

NOTE Confidence: 0.936921758

01:48:07.612 --> 01:48:10.549 be presenting a case of a patient

NOTE Confidence: 0.936921758

01:48:10.549 --> 01:48:13.608 that we have recruited for the kidney

NOTE Confidence: 0.936921758

01:48:13.608 --> 01:48:15.993 Precision Medicine project in Boston.

NOTE Confidence: 0.936921758

01:48:16.000 --> 01:48:18.544 And so most of my time is actually

NOTE Confidence: 0.936921758

01:48:18.544 --> 01:48:21.084 spent doing the Apollo and the

NOTE Confidence: 0.936921758

01:48:21.084 --> 01:48:22.916 kidney Precision Medicine project,

NOTE Confidence: 0.936921758

01:48:22.920 --> 01:48:25.020 but those two projects are mostly in

NOTE Confidence: 0.936921758

01:48:25.020 --> 01:48:26.719 data gathering phase at this point,

NOTE Confidence: 0.936921758

01:48:26.720 --> 01:48:29.100 and so that would be for a

NOTE Confidence: 0.936921758

01:48:29.100 --> 01:48:29.780 future presentation.

NOTE Confidence: 0.936921758

01:48:29.780 --> 01:48:32.433 So this is the basically the standard

NOTE Confidence: 0.936921758

01:48:32.433 --> 01:48:34.600 treatment of diabetic kidney disease.

NOTE Confidence: 0.936921758

01:48:34.600 --> 01:48:37.516 It's blood pressure control trying to

NOTE Confidence: 0.936921758

01:48:37.516 --> 01:48:40.024 lower albuminuria diet interventions as

NOTE Confidence: 0.936921758

01:48:40.024 --> 01:48:42.489 smoking weight and treating complications.

NOTE Confidence: 0.936921758

01:48:42.490 --> 01:48:45.352 And there had really not been

NOTE Confidence: 0.936921758

01:48:45.352 --> 01:48:47.690 any new therapy since 2001.

NOTE Confidence: 0.936921758

01:48:47.690 --> 01:48:50.270 On these two landmark papers were

NOTE Confidence: 0.936921758

01:48:50.270 --> 01:48:52.031 published side-by-side in the

NOTE Confidence: 0.936921758

01:48:52.031 --> 01:48:54.016 New England Journal of Medicine,

NOTE Confidence: 0.936921758

01:48:54.020 --> 01:48:57.122 and that those were the treatment

NOTE Confidence: 0.936921758

01:48:57.122 --> 01:48:58.957 using angiotensin receptor blockers.

NOTE Confidence: 0.936921758

01:48:58.957 --> 01:49:01.591 1 irbesartan 1 Losartan in patients

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NOTE Confidence: 0.936921758

01:49:01.591 --> 01:49:03.810 with type 2 diabetes and that was

NOTE Confidence: 0.936921758

01:49:03.810 --> 01:49:06.124 the the last time that we really had

NOTE Confidence: 0.936921758

01:49:06.124 --> 01:49:08.280 a positive trial in Type 2 diabetes.

NOTE Confidence: 0.936921758

01:49:08.280 --> 01:49:09.720 Many medications followed,

NOTE Confidence: 0.936921758

01:49:09.720 --> 01:49:13.590 all of which turned out to be negative.

NOTE Confidence: 0.936921758

01:49:13.590 --> 01:49:17.150 And so we had two decades of disappointment.

NOTE Confidence: 0.936921758

01:49:17.150 --> 01:49:19.446 And then I'm not going to go

NOTE Confidence: 0.936921758

01:49:19.446 --> 01:49:21.508 over the positive SGLT 2 trials.

NOTE Confidence: 0.936921758

01:49:21.510 --> 01:49:23.358 But since then,

NOTE Confidence: 0.936921758

01:49:23.358 --> 01:49:26.401 we've got multiple SGLT 2 trials

NOTE Confidence: 0.936921758

01:49:26.401 --> 01:49:27.989 that have been positive.

NOTE Confidence: 0.936921758

01:49:27.990 --> 01:49:31.092 And so our algorithm of treatment

NOTE Confidence: 0.936921758

01:49:31.092 --> 01:49:32.126 has shifted.

NOTE Confidence: 0.936921758

01:49:32.130 --> 01:49:34.180 It's still lifestyle is the

NOTE Confidence: 0.936921758

01:49:34.180 --> 01:49:35.410 cornerstone of treatment.

NOTE Confidence: 0.936921758

01:49:35.410 --> 01:49:38.100 But now you can see that the 2022 guide.

NOTE Confidence: 0.936921758

01:49:38.100 --> 01:49:40.822 These are the Cadigal guidelines for the

NOTE Confidence: 0.936921758

01:49:40.822 --> 01:49:43.438 treatment of diabetic kidney disease have.

NOTE Confidence: 0.936921758

01:49:43.440 --> 01:49:45.462 SGLT 2 inhibitors and Ras blockade

NOTE Confidence: 0.936921758

01:49:45.462 --> 01:49:47.765 as first line of therapy for

NOTE Confidence: 0.936921758

01:49:47.765 --> 01:49:49.980 treatment for patients with diabetes

NOTE Confidence: 0.936921758

01:49:49.980 --> 01:49:52.008 and chronic kidney disease and

NOTE Confidence: 0.936921758

01:49:52.008 --> 01:49:54.220 then in the top of the pyramid.

NOTE Confidence: 0.936921758

01:49:54.220 --> 01:49:56.806 Let's say they have goal directed

NOTE Confidence: 0.936921758

01:49:56.806 --> 01:49:58.869 therapy for individuals that

NOTE Confidence: 0.936921758

01:49:58.869 --> 01:50:01.391 perhaps have residual albuminuria.

NOTE Confidence: 0.936921758

01:50:01.391 --> 01:50:07.628 Or are looking for better glycemic control?

NOTE Confidence: 0.936921758

01:50:07.630 --> 01:50:09.660 Using a GLP one inhibitor.

NOTE Confidence: 0.813438656666667

01:50:11.770 --> 01:50:14.024 Receptor agonist, so why do we care

NOTE Confidence: 0.813438656666667

01:50:14.024 --> 01:50:15.870 about residual function or albuminuria?

NOTE Confidence: 0.813438656666667

01:50:15.870 --> 01:50:17.605 And that's because we all

NOTE Confidence: 0.813438656666667

01:50:17.605 --> 01:50:19.690 know that the lower your GFR,

NOTE Confidence: 0.813438656666667

01:50:19.690 --> 01:50:21.670 whether you have diabetes or not,

NOTE Confidence: 0.813438656666667

01:50:21.670 --> 01:50:25.276 you're more likely to have cardiovascular

NOTE Confidence: 0.813438656666667

01:50:25.276 --> 01:50:28.006 morbidity and all cost mortality.

NOTE Confidence: 0.813438656666667

01:50:28.010 --> 01:50:30.971 But it's also very important to note

NOTE Confidence: 0.813438656666667

01:50:30.971 --> 01:50:33.649 that Albuminuria has a similar pattern,

NOTE Confidence: 0.813438656666667

01:50:33.650 --> 01:50:35.189 so this year,

NOTE Confidence: 0.813438656666667

01:50:35.189 --> 01:50:38.267 this last guidelines for the ADA,

NOTE Confidence: 0.813438656666667

01:50:38.270 --> 01:50:41.330 the standards of care which I'm happy to say.

NOTE Confidence: 0.813438656666667

01:50:41.330 --> 01:50:42.610 Also nephrology got upgraded.

NOTE Confidence: 0.813438656666667

01:50:42.610 --> 01:50:44.530 Now we have our own chapter.

NOTE Confidence: 0.813438656666667

01:50:44.530 --> 01:50:47.073 We're not mixed up with ophthalmology

NOTE Confidence: 0.813438656666667

01:50:47.073 --> 01:50:49.788 and neuropathy of microvascular disease,

NOTE Confidence: 0.813438656666667

01:50:49.790 --> 01:50:51.686 but it's been shown they have

NOTE Confidence: 0.813438656666667

01:50:51.686 --> 01:50:53.728 as a therapeutic target that if

NOTE Confidence: 0.813438656666667

01:50:53.728 --> 01:50:55.160 you have severe albuminuria,

NOTE Confidence: 0.813438656666667

01:50:55.160 --> 01:50:57.272 we should try at least to

NOTE Confidence: 0.813438656666667

01:50:57.272 --> 01:50:59.030 lower your albuminuria by 30%.

NOTE Confidence: 0.813438656666667

01:50:59.030 --> 01:51:03.006 That's a based on the trials that have

NOTE Confidence: 0.813438656666667

01:51:03.006 --> 01:51:06.300 been positive with SGLT 2 inhibitors.

NOTE Confidence: 0.813438656666667

01:51:06.300 --> 01:51:09.436 But even though in the data CKD study

NOTE Confidence: 0.813438656666667

01:51:09.436 --> 01:51:12.798 and the Credence study which are the

NOTE Confidence: 0.813438656666667

01:51:12.798 --> 01:51:16.350 two SGLT 2 inhibitor studies that were

NOTE Confidence: 0.813438656666667

01:51:16.350 --> 01:51:19.278 the primary goal was kidney disease

NOTE Confidence: 0.813438656666667

01:51:19.278 --> 01:51:21.800 and that's why I'm presenting those here,

NOTE Confidence: 0.813438656666667

01:51:21.800 --> 01:51:24.089 some of the other studies were looking

NOTE Confidence: 0.813438656666667

01:51:24.089 --> 01:51:26.579 really at a cardiovascular outcomes and

NOTE Confidence: 0.813438656666667

01:51:26.579 --> 01:51:29.459 this the kidney disease was secondary.

NOTE Confidence: 0.813438656666667

01:51:29.460 --> 01:51:32.252 It was really like a finding.

NOTE Confidence: 0.813438656666667

01:51:32.252 --> 01:51:33.580 It was a surprise.

NOTE Confidence: 0.813438656666667

01:51:33.580 --> 01:51:35.204 I don't know that you know it

NOTE Confidence: 0.813438656666667

01:51:35.204 --> 01:51:35.900 wasn't thought that.

NOTE Confidence: 0.813438656666667

01:51:35.900 --> 01:51:37.646 You would have such a big

NOTE Confidence: 0.813438656666667

01:51:37.646 --> 01:51:38.810 impact in kidney disease,

NOTE Confidence: 0.813438656666667

01:51:38.810 --> 01:51:42.310 and so both credence and apathetic KD

NOTE Confidence: 0.813438656666667

01:51:42.310 --> 01:51:44.506 still have a residual kidney function.

NOTE Confidence: 0.813438656666667

01:51:44.510 --> 01:51:46.335 Remember both credence and deposit

NOTE Confidence: 0.813438656666667

01:51:46.335 --> 01:51:48.160 KD to enter the study.

NOTE Confidence: 0.813438656666667

01:51:48.160 --> 01:51:50.505 You had to be on Ras blockade,

NOTE Confidence: 0.813438656666667

01:51:50.510 --> 01:51:52.988 whether it be an ACE inhibitor

NOTE Confidence: 0.813438656666667

01:51:52.988 --> 01:51:55.150 or a or an ARB,

NOTE Confidence: 0.813438656666667

01:51:55.150 --> 01:51:58.097 and therefore we cannot say SGLT 2

NOTE Confidence: 0.813438656666667

01:51:58.097 --> 01:52:00.676 inhibitors are better than race or

NOTE Confidence: 0.813438656666667

01:52:00.676 --> 01:52:03.154 that somehow SGLT 2 inhibitor will

NOTE Confidence: 0.813438656666667

01:52:03.154 --> 01:52:06.276 replace rats because the studies were done.

NOTE Confidence: 0.813438656666667

01:52:06.280 --> 01:52:09.196 On a base of brass inhibition,

NOTE Confidence: 0.813438656666667

01:52:09.200 --> 01:52:12.170 so there is still a significant

NOTE Confidence: 0.813438656666667

01:52:12.170 --> 01:52:13.160 residual risk,

NOTE Confidence: 0.813438656666667

01:52:13.160 --> 01:52:15.145 despite again the positive findings

NOTE Confidence: 0.813438656666667

01:52:15.145 --> 01:52:18.330 of these two studies and and so

NOTE Confidence: 0.813438656666667

01:52:18.330 --> 01:52:20.980 there is an opportunity obviously

NOTE Confidence: 0.813438656666667

01:52:20.980 --> 01:52:24.890 to improve kidney outcomes if we

NOTE Confidence: 0.813438656666667

01:52:24.890 --> 01:52:27.638 have other therapeutic medications.

NOTE Confidence: 0.813438656666667

01:52:27.640 --> 01:52:30.473 And so we know that diabetic

NOTE Confidence: 0.813438656666667

01:52:30.473 --> 01:52:32.538 kidney disease and chronic kidney

NOTE Confidence: 0.813438656666667

01:52:32.538 --> 01:52:34.890 disease in general is associated

NOTE Confidence: 0.813438656666667

01:52:34.890 --> 01:52:36.780 with increased inflammation.

NOTE Confidence: 0.813438656666667

01:52:36.780 --> 01:52:39.216 This is data observational data from the

NOTE Confidence: 0.813438656666667

01:52:39.216 --> 01:52:41.520 quick study using these three markers.

NOTE Confidence: 0.813438656666667

01:52:41.520 --> 01:52:43.794 Fibrinogen TNF alpha and serum albumin

NOTE Confidence: 0.813438656666667

01:52:43.794 --> 01:52:46.228 and basically you can see and I'm

NOTE Confidence: 0.813438656666667

01:52:46.228 --> 01:52:48.669 going to focus on the third model that

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NOTE Confidence: 0.813438656666667

01:52:48.669 --> 01:52:50.594 the higher your inflammatory markers

NOTE Confidence: 0.813438656666667

01:52:50.594 --> 01:52:53.082 the more likely you are to progress

NOTE Confidence: 0.813438656666667

01:52:53.082 --> 01:52:55.673 in the future and you can see that

NOTE Confidence: 0.813438656666667

01:52:55.673 --> 01:52:58.217 in in all the markers and again Sir.

NOTE Confidence: 0.813438656666667

01:52:58.220 --> 01:53:00.255 Albumin has the opposite direction

NOTE Confidence: 0.813438656666667

01:53:00.255 --> 01:53:02.290 because the lower serum albumin

NOTE Confidence: 0.813438656666667

01:53:02.355 --> 01:53:04.327 is associated with inflammation.

NOTE Confidence: 0.813438656666667

01:53:04.330 --> 01:53:05.539 This is data,

NOTE Confidence: 0.813438656666667

01:53:05.539 --> 01:53:07.151 a quick basically recruited

NOTE Confidence: 0.813438656666667

01:53:07.151 --> 01:53:08.360 patients with CKD.

NOTE Confidence: 0.813438656666667

01:53:08.360 --> 01:53:10.515 This is the Framingham offspring

NOTE Confidence: 0.813438656666667

01:53:10.515 --> 01:53:12.670 cohort which has community members

NOTE Confidence: 0.813438656666667

01:53:12.742 --> 01:53:14.740 also looking at the same thing.

NOTE Confidence: 0.813438656666667

01:53:14.740 --> 01:53:16.895 The relationship between GFR and

NOTE Confidence: 0.813438656666667

01:53:16.895 --> 01:53:19.050 inflammation and I'm going to

NOTE Confidence: 0.813438656666667

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01:53:19.122 --> 01:53:21.551 focus just on TNF receptor 2 which

NOTE Confidence: 0.813438656666667

01:53:21.551 --> 01:53:23.602 has been highly associated with

NOTE Confidence: 0.813438656666667

01:53:23.602 --> 01:53:25.466 diabetic kidney disease progression

NOTE Confidence: 0.813438656666667

01:53:25.466 --> 01:53:28.665 and you can see the same thing

NOTE Confidence: 0.813438656666667

01:53:28.665 --> 01:53:31.335 that the individuals that have the

NOTE Confidence: 0.813438656666667

01:53:31.335 --> 01:53:33.820 highest level it had the highest.

NOTE Confidence: 0.813438656666667

01:53:33.820 --> 01:53:37.285 You were also in the highest quartile.

NOTE Confidence: 0.813438656666667

01:53:37.290 --> 01:53:38.970 First statin see.

NOTE Confidence: 0.813438656666667

01:53:38.970 --> 01:53:41.770 So basically confirming what we've

NOTE Confidence: 0.833850814444444

01:53:41.770 --> 01:53:43.414 said before in CKD.

NOTE Confidence: 0.833850814444444

01:53:43.414 --> 01:53:45.469 Also in the general population.

NOTE Confidence: 0.833850814444444

01:53:45.470 --> 01:53:48.560 So we know that a individuals

NOTE Confidence: 0.833850814444444

01:53:48.560 --> 01:53:51.312 with diabetic kidney disease have

NOTE Confidence: 0.833850814444444

01:53:51.312 --> 01:53:53.692 upregulation of the mineralocorticoid

NOTE Confidence: 0.833850814444444

01:53:53.692 --> 01:53:58.010 receptor and in when you have a normal.

NOTE Confidence: 0.833850814444444

01:53:58.010 --> 01:54:01.783 That function, it works in the epithelial

NOTE Confidence: 0.833850814444444

01:54:01.783 --> 01:54:04.320 cell causes electrolyte and water.

NOTE Confidence: 0.833850814444444

01:54:04.320 --> 01:54:07.148 Changes, but it overactivation.

NOTE Confidence: 0.833850814444444

01:54:07.148 --> 01:54:09.269 It creates fibrosis,

NOTE Confidence: 0.833850814444444

01:54:09.270 --> 01:54:11.840 increased oxidative stress and inflammation.

NOTE Confidence: 0.833850814444444

01:54:11.840 --> 01:54:14.120 And this is another picture.

NOTE Confidence: 0.833850814444444

01:54:14.120 --> 01:54:16.129 Sort of depicting this not only in

NOTE Confidence: 0.833850814444444

01:54:16.129 --> 01:54:18.280 the kidney but also vascular damage.

NOTE Confidence: 0.833850814444444

01:54:18.280 --> 01:54:20.264 It causes vascular remodeling,

NOTE Confidence: 0.833850814444444

01:54:20.264 --> 01:54:21.256 endothelial dysfunction,

NOTE Confidence: 0.833850814444444

01:54:21.260 --> 01:54:23.210 also myocardial injury,

NOTE Confidence: 0.833850814444444

01:54:23.210 --> 01:54:25.623 and fibrosis hypertrophy, etcetera.

NOTE Confidence: 0.833850814444444

01:54:25.623 --> 01:54:28.401 So this is an animal study

NOTE Confidence: 0.833850814444444

01:54:28.401 --> 01:54:30.739 that is used for this.

NOTE Confidence: 0.833850814444444

01:54:30.740 --> 01:54:34.450 Looking at inflammation and fibrosis in Iraq.

NOTE Confidence: 0.833850814444444

01:54:34.450 --> 01:54:36.554 Model of aldosterone and

NOTE Confidence: 0.833850814444444

01:54:36.554 --> 01:54:39.184 hypertension and you can see

NOTE Confidence: 0.833850814444444

01:54:39.184 --> 01:54:42.336 here sort of the typical feature,

NOTE Confidence: 0.833850814444444

01:54:42.340 --> 01:54:44.340 some vascular and glomerular damage.

NOTE Confidence: 0.833850814444444

01:54:44.340 --> 01:54:45.740 Leukocyte infiltration,

NOTE Confidence: 0.833850814444444

01:54:45.740 --> 01:54:47.840 protein cast etcetera.

NOTE Confidence: 0.833850814444444

01:54:47.840 --> 01:54:49.328 But also very important to note

NOTE Confidence: 0.833850814444444

01:54:49.328 --> 01:54:51.232 that in the renal color text when

NOTE Confidence: 0.833850814444444

01:54:51.232 --> 01:54:52.657 they looked at messenger RNA,

NOTE Confidence: 0.833850814444444

01:54:52.660 --> 01:54:54.585 the levels of the proinflammatory

NOTE Confidence: 0.833850814444444

01:54:54.585 --> 01:54:56.680 genes in these animals was

NOTE Confidence: 0.833850814444444

01:54:56.680 --> 01:54:59.030 higher in those individuals that

NOTE Confidence: 0.833850814444444

01:54:59.030 --> 01:55:01.460 had the highest aldosterone.

NOTE Confidence: 0.919110223333333

01:55:03.630 --> 01:55:06.889 And so when you have this, not when you

NOTE Confidence: 0.919110223333333

01:55:06.889 --> 01:55:09.069 have knockout animals, then it went.

NOTE Confidence: 0.919110223333333

01:55:09.069 --> 01:55:11.510 This is and feed them at Western diet.

NOTE Confidence: 0.919110223333333

01:55:11.510 --> 01:55:15.224 That's what WD means. And these

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NOTE Confidence: 0.919110223333333

01:55:15.224 --> 01:55:18.090 animals have endothelial specific Mr.

NOTE Confidence: 0.919110223333333

01:55:18.090 --> 01:55:20.106 Knockout when they looked at their

NOTE Confidence: 0.919110223333333

01:55:20.106 --> 01:55:22.185 kidneys they could see even though

NOTE Confidence: 0.919110223333333

01:55:22.185 --> 01:55:23.870 they're in the Western diet.

NOTE Confidence: 0.919110223333333

01:55:23.870 --> 01:55:25.742 If you don't, this is Western

NOTE Confidence: 0.919110223333333

01:55:25.742 --> 01:55:26.990 diet without the knockout.

NOTE Confidence: 0.919110223333333

01:55:26.990 --> 01:55:29.594 This is Western diet with the knockout

NOTE Confidence: 0.919110223333333

01:55:29.594 --> 01:55:33.394 and you can see that if you have the.

NOTE Confidence: 0.919110223333333

01:55:33.394 --> 01:55:36.917 The Western diet with the knockout you

NOTE Confidence: 0.919110223333333

01:55:36.917 --> 01:55:40.298 have the same findings of fibrosis as

NOTE Confidence: 0.919110223333333

01:55:40.298 --> 01:55:45.110 if you were not on the Western diet.

NOTE Confidence: 0.919110223333333

01:55:45.110 --> 01:55:46.785 And and here's this fibrosis

NOTE Confidence: 0.919110223333333

01:55:46.785 --> 01:55:47.790 in the interstitium.

NOTE Confidence: 0.919110223333333

01:55:47.790 --> 01:55:51.408 Here's periarterial fibrosis.

NOTE Confidence: 0.919110223333333

01:55:51.410 --> 01:55:53.150 And this is now human data,

NOTE Confidence: 0.919110223333333

185

01:55:53.150 --> 01:55:56.280 so this is data from 2005 but

NOTE Confidence: 0.919110223333333

01:55:56.280 --> 01:55:58.380 still relevant showing these

NOTE Confidence: 0.919110223333333

01:55:58.380 --> 01:56:01.295 were 95 patients that had kidney

NOTE Confidence: 0.919110223333333

01:56:01.295 --> 01:56:03.203 biopsies and aldosterone measured.

NOTE Confidence: 0.919110223333333

01:56:03.210 --> 01:56:06.100 And if you can see that in the X axis

NOTE Confidence: 0.919110223333333

01:56:06.182 --> 01:56:09.304 they creatinine clearance in the Y axis,

NOTE Confidence: 0.919110223333333

01:56:09.310 --> 01:56:11.620 the serum aldosterone level and

NOTE Confidence: 0.919110223333333

01:56:11.620 --> 01:56:14.988 you can see that the lower your

NOTE Confidence: 0.919110223333333

01:56:14.988 --> 01:56:17.868 GFR your aldosterone was higher and

NOTE Confidence: 0.919110223333333

01:56:17.868 --> 01:56:21.060 also in looking at the biopsies.

NOTE Confidence: 0.919110223333333

01:56:21.060 --> 01:56:23.664 In the percent scarring in the X

NOTE Confidence: 0.919110223333333

01:56:23.664 --> 01:56:25.908 axis and aldosterone and the Y axis,

NOTE Confidence: 0.919110223333333

01:56:25.910 --> 01:56:30.222 you can see that the more higher your

NOTE Confidence: 0.919110223333333

01:56:30.222 --> 01:56:34.327 fibrosis the higher your aldosterone.

NOTE Confidence: 0.919110223333333

01:56:34.330 --> 01:56:35.725 So in summary,

NOTE Confidence: 0.919110223333333

01:56:35.725 --> 01:56:38.515 there again a multiple animal studies,

NOTE Confidence: 0.919110223333333

01:56:38.520 --> 01:56:39.668 but I'm going to focus on this.

NOTE Confidence: 0.919110223333333

01:56:39.670 --> 01:56:41.596 There's significant evidence

NOTE Confidence: 0.919110223333333

01:56:41.596 --> 01:56:44.164 that it creating Mr.

NOTE Confidence: 0.919110223333333

01:56:44.170 --> 01:56:46.960 Knockouts basically spares the organs

NOTE Confidence: 0.919110223333333

01:56:46.960 --> 01:56:50.490 either the heart or the kidney,

NOTE Confidence: 0.919110223333333

01:56:50.490 --> 01:56:53.328 or the blood vessels from fibrosis,

NOTE Confidence: 0.919110223333333

01:56:53.330 --> 01:56:54.038 inflammation, etcetera.

NOTE Confidence: 0.919110223333333

01:56:54.038 --> 01:56:57.490 And we know that in the setting of diabetes,

NOTE Confidence: 0.919110223333333

01:56:57.490 --> 01:56:58.858 disease, kidney disease,

NOTE Confidence: 0.919110223333333

01:56:58.858 --> 01:57:00.898 heart failure, cardiovascular disease,

NOTE Confidence: 0.919110223333333

01:57:00.898 --> 01:57:03.718 all of these diseases and.

NOTE Confidence: 0.919110223333333

01:57:03.720 --> 01:57:04.736 To be quite honest,

NOTE Confidence: 0.919110223333333

01:57:04.736 --> 01:57:06.260 in the patients that I see,

NOTE Confidence: 0.919110223333333

01:57:06.260 --> 01:57:07.996 most of them have all of them.

NOTE Confidence: 0.919110223333333

01:57:08.000 --> 01:57:09.920 They they're severe overactivation

NOTE Confidence: 0.919110223333333

01:57:09.920 --> 01:57:11.840 of the MMR system.

NOTE Confidence: 0.919110223333333

01:57:11.840 --> 01:57:13.928 So in summary it is chronic

NOTE Confidence: 0.919110223333333

01:57:13.928 --> 01:57:15.320 kidney disease associated with

NOTE Confidence: 0.919110223333333

01:57:15.380 --> 01:57:16.940 inflammation and fibrosis.

NOTE Confidence: 0.919110223333333

01:57:16.940 --> 01:57:19.025 The more advanced chronic kidney

NOTE Confidence: 0.919110223333333

01:57:19.025 --> 01:57:21.110 disease is associated with increased

NOTE Confidence: 0.919110223333333

01:57:21.178 --> 01:57:23.243 inflammation and fibrosis and the

NOTE Confidence: 0.919110223333333

01:57:23.243 --> 01:57:24.755 mineral mineral corticoid receptor

NOTE Confidence: 0.919110223333333

01:57:24.755 --> 01:57:26.580 is involved in the regulation

NOTE Confidence: 0.919110223333333

01:57:26.580 --> 01:57:28.019 of inflammation and fibrosis,

NOTE Confidence: 0.919110223333333

01:57:28.020 --> 01:57:30.900 and this overactivation is what causes

NOTE Confidence: 0.919110223333333

01:57:30.900 --> 01:57:32.820 kidney and cardiovascular damage.

NOTE Confidence: 0.919110223333333

01:57:32.820 --> 01:57:34.830 And here's where this molecule.

NOTE Confidence: 0.919110223333333

01:57:34.830 --> 01:57:37.300 Comes along initially it was

NOTE Confidence: 0.919110223333333

01:57:37.300 --> 01:57:39.247 called Bay 9488 sixty two.

NOTE Confidence: 0.919110223333333

01:57:39.247 --> 01:57:41.480 I'm assuming the Bay comes from Bayer,

NOTE Confidence: 0.919110223333333

01:57:41.480 --> 01:57:44.000 and the later was renamed as Finerenone

NOTE Confidence: 0.919110223333333

01:57:44.000 --> 01:57:46.463 and this is the chemical structure

NOTE Confidence: 0.919110223333333

01:57:46.463 --> 01:57:48.648 and the difference between this

NOTE Confidence: 0.919110223333333

01:57:48.648 --> 01:57:50.772 and our previous mineralocorticoid

NOTE Confidence: 0.919110223333333

01:57:50.772 --> 01:57:53.702 receptor antagonist is that FINERENONE

NOTE Confidence: 0.919110223333333

01:57:53.702 --> 01:57:56.772 has a significant higher affinity

NOTE Confidence: 0.919110223333333

01:57:56.772 --> 01:57:59.396 to the mineralocorticoid receptor,

NOTE Confidence: 0.919110223333333

01:57:59.400 --> 01:58:01.920 and the other difference is that it

NOTE Confidence: 0.919110223333333

01:58:01.920 --> 01:58:04.572 it's not renally excreted, and those.

NOTE Confidence: 0.919110223333333

01:58:04.572 --> 01:58:08.060 Qualities and made made it at the time.

NOTE Confidence: 0.919110223333333

01:58:08.060 --> 01:58:10.586 Think that they would have less

NOTE Confidence: 0.919110223333333

01:58:10.586 --> 01:58:13.436 of the known complications of the

NOTE Confidence: 0.919110223333333

01:58:13.436 --> 01:58:16.291 other MRA which are gynecomastia.

NOTE Confidence: 0.919110223333333

01:58:16.291 --> 01:58:17.333 Hypogastrium mostly,

NOTE Confidence: 0.919110223333333

01:58:17.333 --> 01:58:20.459 and so these are the initial

NOTE Confidence: 0.919110223333333

01:58:20.459 --> 01:58:22.987 trials using the different doses,

NOTE Confidence: 0.919110223333333

01:58:22.990 --> 01:58:27.973 the 1.125 and and 20 but just basically

NOTE Confidence: 0.919110223333333

01:58:27.973 --> 01:58:31.138 showing you that there's really a

NOTE Confidence: 0.919110223333333

01:58:31.138 --> 01:58:35.478 some change as soon as you give it on a.

NOTE Confidence: 0.919110223333333

01:58:35.480 --> 01:58:36.938 GFR very minimal,

NOTE Confidence: 0.919110223333333

01:58:36.938 --> 01:58:40.340 and it doesn't really vary by dose

NOTE Confidence: 0.919110223333333

01:58:40.439 --> 01:58:43.504 and the potassium level stayed

NOTE Confidence: 0.919110223333333

01:58:43.504 --> 01:58:45.956 relatively stable over time,

NOTE Confidence: 0.919110223333333

01:58:45.960 --> 01:58:48.000 and the systolic blood pressure.

NOTE Confidence: 0.850244851

01:58:48.000 --> 01:58:50.724 It really. It's not the best

NOTE Confidence: 0.850244851

01:58:50.724 --> 01:58:52.540 systolic blood pressure medication,

NOTE Confidence: 0.850244851

01:58:52.540 --> 01:58:54.900 so it it lowers it a little bit,

NOTE Confidence: 0.850244851

01:58:54.900 --> 01:58:58.170 but not anything very impressive.

NOTE Confidence: 0.850244851

01:58:58.170 --> 01:59:00.732 Is so these are data from credence

NOTE Confidence: 0.850244851

01:59:00.732 --> 01:59:03.045 and I just want to mention

NOTE Confidence: 0.850244851

01:59:03.045 --> 01:59:05.670 the year this is 2015 to 2018.

NOTE Confidence: 0.850244851

01:59:05.670 --> 01:59:09.163 So SGLT 2 inhibitor was available but

NOTE Confidence: 0.850244851

01:59:09.163 --> 01:59:12.926 not as commonly used as it is nowadays.

NOTE Confidence: 0.850244851

01:59:12.930 --> 01:59:15.962 So in the fidelity of study which was

NOTE Confidence: 0.850244851

01:59:15.962 --> 01:59:19.169 the one that had the kidney outcome,

NOTE Confidence: 0.850244851

01:59:19.170 --> 01:59:21.246 the figural study was the sister

NOTE Confidence: 0.850244851

01:59:21.246 --> 01:59:23.187 study that had the cardiovascular

NOTE Confidence: 0.850244851

01:59:23.187 --> 01:59:25.617 outcome as the main outcome.

NOTE Confidence: 0.850244851

01:59:25.620 --> 01:59:27.270 You and then they switch

NOTE Confidence: 0.850244851

01:59:27.270 --> 01:59:28.260 for secondary outcomes,

NOTE Confidence: 0.850244851

01:59:28.260 --> 01:59:32.640 but basically 13 almost 14,000 individuals

NOTE Confidence: 0.850244851

01:59:32.640 --> 01:59:36.243 were enrolled and 5700 were randomized.

NOTE Confidence: 0.850244851

01:59:36.243 --> 01:59:38.598 The randomization was to either

NOTE Confidence: 0.850244851

01:59:38.598 --> 01:59:41.580 10 or funeral or 20 of finerenone

NOTE Confidence: 0.850244851

01:59:41.580 --> 01:59:44.752 based on your GFR and then you know

NOTE Confidence: 0.850244851

01:59:44.752 --> 01:59:47.188 you had your visits like this.

NOTE Confidence: 0.850244851

01:59:47.190 --> 01:59:48.786 And these are the final studies.

NOTE Confidence: 0.850244851

01:59:48.790 --> 01:59:51.268 This was published about two years ago

NOTE Confidence: 0.850244851

01:59:51.268 --> 01:59:54.747 and you can see that it was a positive study,

NOTE Confidence: 0.850244851

01:59:54.750 --> 01:59:56.652 meaning that there was a decrease

NOTE Confidence: 0.850244851

01:59:56.652 --> 01:59:58.470 in the primary composite outcomes.

NOTE Confidence: 0.850244851

01:59:58.470 --> 02:00:02.390 And in this study the primary composite

NOTE Confidence: 0.850244851

02:00:02.390 --> 02:00:06.609 outcome was a decrease in GFR of 40%.

NOTE Confidence: 0.850244851

02:00:06.610 --> 02:00:11.218 Going on dialysis or death from a renal cost.

NOTE Confidence: 0.850244851

02:00:11.220 --> 02:00:13.908 And here you can see the primary

NOTE Confidence: 0.850244851

02:00:13.908 --> 02:00:15.889 kidney failure was end stage,

NOTE Confidence: 0.850244851

02:00:15.890 --> 02:00:18.620 kidney disease, or GFR less than 15.

NOTE Confidence: 0.850244851

02:00:18.620 --> 02:00:22.634 This is the 40% decrease death of renal cost.

NOTE Confidence: 0.850244851

02:00:22.640 --> 02:00:25.064 And so the this is the same picture

NOTE Confidence: 0.850244851

02:00:25.064 --> 02:00:26.917 just depicted in a different way.

NOTE Confidence: 0.850244851

02:00:26.920 --> 02:00:29.600 But showing us the sort of the breakdown.

NOTE Confidence: 0.850244851

02:00:29.600 --> 02:00:34.001 But you can see that all of them favored

NOTE Confidence: 0.850244851

02:00:34.001 --> 02:00:37.664 finerenone use and this the secondary

NOTE Confidence: 0.850244851

02:00:37.664 --> 02:00:41.220 outcomes were cardiovascular and they key.

NOTE Confidence: 0.850244851

02:00:41.220 --> 02:00:43.430 Secondary outcome was positive again.

NOTE Confidence: 0.850244851

02:00:43.430 --> 02:00:46.410 Some of them because of.

NOTE Confidence: 0.850244851

02:00:46.410 --> 02:00:49.210 Numbers it did not reach

NOTE Confidence: 0.850244851

02:00:49.210 --> 02:00:50.890 individuals is significant.

NOTE Confidence: 0.850244851

02:00:50.890 --> 02:00:54.370 We can see that from early on the

NOTE Confidence: 0.850244851

02:00:54.370 --> 02:00:58.623 decrease in Albuminuria was still quite a

NOTE Confidence: 0.850244851

02:00:58.623 --> 02:01:02.590 substantial and leveled throughout the study.

NOTE Confidence: 0.850244851

02:01:02.590 --> 02:01:05.056 And same as SGLT 2 inhibitors,

NOTE Confidence: 0.850244851

02:01:05.060 --> 02:01:07.600 there's always that early decline

NOTE Confidence: 0.850244851

02:01:07.600 --> 02:01:11.288 in GFR and by in using finerenone

NOTE Confidence: 0.850244851

02:01:11.288 --> 02:01:15.440 in by month 24 or two years later,

NOTE Confidence: 0.850244851

02:01:15.440 --> 02:01:19.310 that's when you start really seeing

NOTE Confidence: 0.850244851

02:01:19.310 --> 02:01:21.301 the picture separate.

NOTE Confidence: 0.850244851

02:01:21.301 --> 02:01:24.806 So there's this early decline,

NOTE Confidence: 0.850244851

02:01:24.810 --> 02:01:27.449 and then this sort of long slope

NOTE Confidence: 0.850244851

02:01:27.449 --> 02:01:29.730 that is shows a difference.

NOTE Confidence: 0.850244851

02:01:29.730 --> 02:01:31.142 And then very importantly,

NOTE Confidence: 0.850244851

02:01:31.142 --> 02:01:33.260 this is what we're talking about.

NOTE Confidence: 0.850244851

02:01:33.260 --> 02:01:36.136 This potassium in individuals

NOTE Confidence: 0.850244851

02:01:36.136 --> 02:01:39.731 using finerenone did have higher

NOTE Confidence: 0.850244851

02:01:39.731 --> 02:01:41.734 potassium than the placebo arm,

NOTE Confidence: 0.850244851

02:01:41.734 --> 02:01:44.550 but it did not reach any significant

NOTE Confidence: 0.850244851

02:01:44.550 --> 02:01:47.010 statistical significant difference.

NOTE Confidence: 0.850244851

02:01:47.010 --> 02:01:49.607 But if you look at the supplement,

NOTE Confidence: 0.850244851

02:01:49.610 --> 02:01:52.753 you can see that they do discuss

NOTE Confidence: 0.850244851

02:01:52.753 --> 02:01:55.754 that five point you know 21% of

NOTE Confidence: 0.850244851

02:01:55.754 --> 02:01:57.764 people on the finerenone group

NOTE Confidence: 0.850244851

02:01:57.764 --> 02:01:59.719 had potassium greater than five.

NOTE Confidence: 0.850244851

02:01:59.720 --> 02:02:01.530 And five compared to placebo,

194

NOTE Confidence: 0.850244851

02:02:01.530 --> 02:02:05.498 which was almost 10% but that severe high

NOTE Confidence: 0.850244851

02:02:05.498 --> 02:02:08.600 potassium greater than six was still seen.

NOTE Confidence: 0.850244851

02:02:08.600 --> 02:02:09.144 You know,

NOTE Confidence: 0.850244851

02:02:09.144 --> 02:02:11.320 an almost two to three times higher in

NOTE Confidence: 0.850244851

02:02:11.384 --> 02:02:14.092 the Finerenone Group 4.5 versus 1.4.

NOTE Confidence: 0.850244851

02:02:14.092 --> 02:02:18.120 So it's still important to monitor the

NOTE Confidence: 0.850244851

02:02:18.120 --> 02:02:21.640 potassium after starting treatment.

NOTE Confidence: 0.850244851

02:02:21.640 --> 02:02:25.762 So what we did is it.

NOTE Confidence: 0.850244851

02:02:25.762 --> 02:02:28.054 It was a pre specified goal.

NOTE Confidence: 0.850244851

02:02:28.060 --> 02:02:30.130 We merge both the fidelity.

NOTE Confidence: 0.850244851

02:02:30.130 --> 02:02:32.098 And the Figaro trials,

NOTE Confidence: 0.850244851

02:02:32.098 --> 02:02:35.575 because they had exactly the same visit,

NOTE Confidence: 0.850244851

02:02:35.575 --> 02:02:38.725 and they have different entry criteria,

NOTE Confidence: 0.9233272

02:02:38.730 --> 02:02:43.000 but. We combined the studies and

NOTE Confidence: 0.9233272

02:02:43.000 --> 02:02:45.979 now it becomes the largest study

NOTE Confidence: 0.9233272

02:02:45.979 --> 02:02:48.784 in patients with chronic kidney

NOTE Confidence: 0.9233272

02:02:48.784 --> 02:02:51.484 disease because now there's 13,026

NOTE Confidence: 0.9233272

02:02:51.484 --> 02:02:53.754 patients that were randomized and

NOTE Confidence: 0.9233272

02:02:53.754 --> 02:02:56.729 a medium follow up of three years

NOTE Confidence: 0.9233272

02:02:56.730 --> 02:03:00.522 and you can see in this picture sort

NOTE Confidence: 0.9233272

02:03:00.522 --> 02:03:04.056 of what areas of CKD it covers.

NOTE Confidence: 0.9233272

02:03:04.060 --> 02:03:04.907 I don't know if you see it,

NOTE Confidence: 0.9233272

02:03:04.910 --> 02:03:07.534 it's a little bit sort of a blue

NOTE Confidence: 0.9233272

02:03:07.534 --> 02:03:09.390 darker color here, but basically

NOTE Confidence: 0.9233272

02:03:09.390 --> 02:03:11.290 all the individuals with severe.

NOTE Confidence: 0.9233272

02:03:11.290 --> 02:03:14.668 CKD, and here with moderate seeking

NOTE Confidence: 0.9233272

02:03:14.668 --> 02:03:16.920 and with moderate albuminuria,

NOTE Confidence: 0.9233272

02:03:16.920 --> 02:03:19.026 sorry and then these are the

NOTE Confidence: 0.9233272

02:03:19.026 --> 02:03:20.882 key inclusion criteria and key

NOTE Confidence: 0.9233272

02:03:20.882 --> 02:03:22.797 exclusion criteria of the study.

NOTE Confidence: 0.9233272

02:03:22.800 --> 02:03:24.120 Basically like I said,

NOTE Confidence: 0.9233272

02:03:24.120 --> 02:03:26.578 individuals had to be on the maximum

NOTE Confidence: 0.9233272

02:03:26.578 --> 02:03:29.026 tolerated those that's a little bit

NOTE Confidence: 0.9233272

02:03:29.026 --> 02:03:31.406 also different from the SGLT 2 trials

NOTE Confidence: 0.9233272

02:03:31.406 --> 02:03:34.378 where you just had to be on an ace or an ARB.

NOTE Confidence: 0.9233272

02:03:34.380 --> 02:03:36.543 You did not have to be on

NOTE Confidence: 0.9233272

02:03:36.543 --> 02:03:37.870 the maximum tolerated dose.

NOTE Confidence: 0.9233272

02:03:37.870 --> 02:03:40.440 And OK.

NOTE Confidence: 0.9233272

02:03:40.440 --> 02:03:41.727 So in summary,

NOTE Confidence: 0.9233272

02:03:41.727 --> 02:03:44.730 I already discussed that funeral known it

NOTE Confidence: 0.9233272

02:03:44.816 --> 02:03:48.036 was novel selective and non steroidal MRA.

NOTE Confidence: 0.9233272

02:03:48.040 --> 02:03:50.080 That fidelity is approved.

NOTE Confidence: 0.9233272

02:03:50.080 --> 02:03:52.630 Specified pool analysis of both

NOTE Confidence: 0.9233272

02:03:52.630 --> 02:03:54.891 studies and when they combine

NOTE Confidence: 0.9233272

02:03:54.891 --> 02:03:57.393 the studies and you'll see this.

NOTE Confidence: 0.9233272

02:03:57.400 --> 02:04:00.580 This was also already published and

NOTE Confidence: 0.9233272

02:04:00.580 --> 02:04:04.395 they combined outcomes was 14% risk

NOTE Confidence: 0.9233272

02:04:04.395 --> 02:04:06.970 reduction in the cardiovascular composite

NOTE Confidence: 0.9233272

02:04:06.970 --> 02:04:10.270 Antone and 23% in the kidney composite.

NOTE Confidence: 0.9233272

02:04:10.270 --> 02:04:11.270 Two point,

NOTE Confidence: 0.9233272

02:04:11.270 --> 02:04:14.270 but contrary to the previous publications,

NOTE Confidence: 0.9233272

02:04:14.270 --> 02:04:17.230 they had used 40% in the new publication,

NOTE Confidence: 0.9233272

02:04:17.230 --> 02:04:20.958 merging the two data sets you can look

NOTE Confidence: 0.9233272

02:04:20.958 --> 02:04:24.982 at it a you know a less common outcome,

NOTE Confidence: 0.9233272

02:04:24.982 --> 02:04:27.238 which was 57%.

NOTE Confidence: 0.9233272

02:04:27.240 --> 02:04:29.616 So I initially we obviously wanted

NOTE Confidence: 0.9233272

02:04:29.616 --> 02:04:32.565 to know if there was any improvement

NOTE Confidence: 0.9233272

02:04:32.565 --> 02:04:35.554 in those patients that were both on

NOTE Confidence: 0.9233272

02:04:35.638 --> 02:04:38.516 finer and SGLT 2 treatment and so

NOTE Confidence: 0.9233272

02:04:38.516 --> 02:04:41.512 it combining the two data sets that

NOTE Confidence: 0.9233272

02:04:41.512 --> 02:04:44.961 allows us to do that and there is

NOTE Confidence: 0.9233272

02:04:44.961 --> 02:04:47.461 some preclinical data showing and

NOTE Confidence: 0.9233272

02:04:47.461 --> 02:04:51.789 here you can see it that these were.

NOTE Confidence: 0.9233272

02:04:51.790 --> 02:04:54.796 And but these were animals on

NOTE Confidence: 0.9233272

02:04:54.796 --> 02:04:57.268 empagliflozin finerenone and then a

NOTE Confidence: 0.9233272

02:04:57.268 --> 02:04:59.560 group that were in combination and

NOTE Confidence: 0.9233272

02:04:59.560 --> 02:05:02.460 you can see and these are hearts.

NOTE Confidence: 0.9233272

02:05:02.460 --> 02:05:05.012 They looked at cardiac fibrosis,

NOTE Confidence: 0.9233272

02:05:05.012 --> 02:05:08.220 but you can see this is the scoring

NOTE Confidence: 0.9233272

02:05:08.304 --> 02:05:09.290 for fibrosis.

NOTE Confidence: 0.9233272

02:05:09.290 --> 02:05:12.020 But you can see that there was

NOTE Confidence: 0.9233272

02:05:12.020 --> 02:05:14.171 some preliminary data that in

NOTE Confidence: 0.9233272

02:05:14.171 --> 02:05:16.421 the combination of both perhaps

NOTE Confidence: 0.9233272

02:05:16.421 --> 02:05:18.530 would have decreased fibrosis.

NOTE Confidence: 0.9233272

02:05:18.530 --> 02:05:20.861 And there was also great a survival

NOTE Confidence: 0.9233272

02:05:20.861 --> 02:05:23.438 benefit in the in the animals that

NOTE Confidence: 0.9233272

02:05:23.438 --> 02:05:25.323 had both empire and finerenone,

NOTE Confidence: 0.9233272

02:05:25.330 --> 02:05:29.137 and that is this this the survival a graph.

NOTE Confidence: 0.9233272

02:05:29.140 --> 02:05:31.642 OK the green is the combination

NOTE Confidence: 0.9233272

02:05:31.642 --> 02:05:34.040 therapy and black is placebo.

NOTE Confidence: 0.9233272

02:05:34.040 --> 02:05:36.374 So finerenone and empower about the

NOTE Confidence: 0.9233272

02:05:36.374 --> 02:05:38.700 same and then combination was better.

NOTE Confidence: 0.9233272

02:05:38.700 --> 02:05:39.720 Placebo was worse.

NOTE Confidence: 0.687284509

02:05:41.850 --> 02:05:45.186 And so this is the trial

NOTE Confidence: 0.687284509

02:05:45.190 --> 02:05:48.310 from all those patients.

NOTE Confidence: 0.687284509

02:05:48.310 --> 02:05:51.970 Only 877 participants, where on an

NOTE Confidence: 0.687284509

02:05:51.970 --> 02:05:55.925 SGLT 2 inhibitor during the trial and

NOTE Confidence: 0.687284509

02:05:55.925 --> 02:05:59.306 and so that is important to note.

NOTE Confidence: 0.687284509

02:05:59.310 --> 02:06:02.054 So I remember. I told you that

NOTE Confidence: 0.687284509

02:06:02.054 --> 02:06:03.950 the study finished in 2018.

NOTE Confidence: 0.687284509

02:06:03.950 --> 02:06:07.334 So at that time is some of the SGLT

NOTE Confidence: 0.687284509

02:06:07.334 --> 02:06:11.378 2 trials had not come out yet and so.

NOTE Confidence: 0.687284509

02:06:11.380 --> 02:06:12.488 That's probably why not

NOTE Confidence: 0.687284509

02:06:12.488 --> 02:06:13.873 more people were on it.

NOTE Confidence: 0.687284509

02:06:13.880 --> 02:06:15.725 But there are other important

NOTE Confidence: 0.687284509

02:06:15.725 --> 02:06:17.942 difference are that people that were

NOTE Confidence: 0.687284509

02:06:17.942 --> 02:06:20.063 on SGLT 2 inhibitors were also more

NOTE Confidence: 0.687284509

02:06:20.063 --> 02:06:22.151 likely to be on statins and they

NOTE Confidence: 0.687284509

02:06:22.151 --> 02:06:25.026 were also more likely to be on GLP.

NOTE Confidence: 0.687284509

02:06:25.026 --> 02:06:27.436 One receptor agonist so GLP

NOTE Confidence: 0.687284509

02:06:27.436 --> 02:06:29.884 one receptor agonist required

NOTE Confidence: 0.687284509

02:06:29.884 --> 02:06:33.216 injections and therefore it poses

NOTE Confidence: 0.687284509

02:06:33.216 --> 02:06:35.996 the theoretical option that perhaps

NOTE Confidence: 0.687284509

02:06:35.996 --> 02:06:39.245 this is these patients with SLE

NOTE Confidence: 0.687284509

02:06:39.245 --> 02:06:42.047 on SGLT 2 inhibitors were perhaps.

NOTE Confidence: 0.687284509

02:06:42.050 --> 02:06:44.935 Either more difficult to control

NOTE Confidence: 0.687284509

02:06:44.935 --> 02:06:47.243 individuals or individuals that

NOTE Confidence: 0.687284509

02:06:47.243 --> 02:06:50.088 were with physicians that were,

NOTE Confidence: 0.687284509

02:06:50.090 --> 02:06:54.728 let's say, more aggressive or more.

NOTE Confidence: 0.687284509

02:06:54.730 --> 02:06:55.820 Willing to.

NOTE Confidence: 0.893456377272727

02:06:57.840 --> 02:07:00.070 Give this medications that perhaps

NOTE Confidence: 0.893456377272727

02:07:00.070 --> 02:07:02.740 we're not mainstream at the time,

NOTE Confidence: 0.893456377272727

02:07:02.740 --> 02:07:04.940 so anyway, so the the GFR was a

NOTE Confidence: 0.893456377272727

02:07:04.940 --> 02:07:07.073 little bit higher in those individuals

NOTE Confidence: 0.893456377272727

02:07:07.073 --> 02:07:09.347 that were on SGLT 2 inhibitors

NOTE Confidence: 0.893456377272727

02:07:09.422 --> 02:07:11.774 compared to the others that you ACR.

NOTE Confidence: 0.893456377272727

02:07:11.780 --> 02:07:13.544 I don't really think that there's

NOTE Confidence: 0.893456377272727

02:07:13.544 --> 02:07:15.400 a big difference here. And.

NOTE Confidence: 0.730639867142857

02:07:17.550 --> 02:07:21.085 And but we we found out again,

NOTE Confidence: 0.730639867142857

02:07:21.090 --> 02:07:24.167 just highlighting that only six point 7% of

NOTE Confidence: 0.730639867142857

02:07:24.167 --> 02:07:26.863 the individuals it were an SGLT 2 inhibitor.

NOTE Confidence: 0.730639867142857

02:07:26.870 --> 02:07:32.032 So the power of this is not the best,

NOTE Confidence: 0.730639867142857

02:07:32.032 --> 02:07:35.560 but we can see that there was significant

NOTE Confidence: 0.730639867142857

02:07:35.653 --> 02:07:38.767 reduction in a in those individuals.

NOTE Confidence: 0.730639867142857

02:07:38.770 --> 02:07:42.950 Those that were on SGLT 2 or not SGLT 2

NOTE Confidence: 0.730639867142857

02:07:43.061 --> 02:07:47.027 they had the same similar reductions.

NOTE Confidence: 0.730639867142857

02:07:47.030 --> 02:07:48.506 If you were not an SGLT.

NOTE Confidence: 0.730639867142857

02:07:48.510 --> 02:07:50.310 To inhibitors with 32%.

NOTE Confidence: 0.730639867142857

02:07:50.310 --> 02:07:55.860 If you were on SGLT 2 inhibitor of 37%.

NOTE Confidence: 0.730639867142857

02:07:55.860 --> 02:08:01.870 This data was presented at ADA last year.

NOTE Confidence: 0.730639867142857

02:08:01.870 --> 02:08:05.372 And then we looked at cardiovascular

NOTE Confidence: 0.730639867142857

02:08:05.372 --> 02:08:07.520 benefit and you can see that

NOTE Confidence: 0.730639867142857

02:08:07.584 --> 02:08:09.309 the cardiovascular benefit.

NOTE Confidence: 0.730639867142857

02:08:09.310 --> 02:08:12.120 Again, the hazard ratio had

NOTE Confidence: 0.730639867142857

02:08:12.120 --> 02:08:13.806 wider confidence intervals,

NOTE Confidence: 0.730639867142857

02:08:13.810 --> 02:08:17.248 but you can see that it was positive whether

NOTE Confidence: 0.730639867142857

02:08:17.248 --> 02:08:20.260 you wear an SGLT 2 inhibitor or not.

NOTE Confidence: 0.730639867142857

02:08:20.260 --> 02:08:22.738 And there was no interaction about.

NOTE Confidence: 0.730639867142857

02:08:22.740 --> 02:08:24.420 You know whether you were an

NOTE Confidence: 0.730639867142857

02:08:24.420 --> 02:08:25.840 SGLT 2 inhibitor or not,

NOTE Confidence: 0.730639867142857

02:08:25.840 --> 02:08:27.040 and then more specifically,

NOTE Confidence: 0.730639867142857

02:08:27.040 --> 02:08:29.284 as as you know, our patients are

NOTE Confidence: 0.730639867142857

02:08:29.284 --> 02:08:31.372 more likely to develop heart failure.

NOTE Confidence: 0.730639867142857

02:08:31.380 --> 02:08:34.060 So we looked at that.

NOTE Confidence: 0.730639867142857

02:08:34.060 --> 02:08:36.765 Individually and you can see

NOTE Confidence: 0.730639867142857

02:08:36.765 --> 02:08:40.310 similarly that there wasn't a benefit.

NOTE Confidence: 0.730639867142857

02:08:40.310 --> 02:08:43.595 The interaction did not reach

NOTE Confidence: 0.730639867142857

02:08:43.595 --> 02:08:44.909 significance either,

NOTE Confidence: 0.730639867142857

02:08:44.910 --> 02:08:46.410 so there was no difference.

NOTE Confidence: 0.730639867142857

02:08:46.410 --> 02:08:48.307 We never known work the same whether

NOTE Confidence: 0.730639867142857

02:08:48.307 --> 02:08:50.706 you were on an SGLT 2 inhibitor or not.

NOTE Confidence: 0.730639867142857

02:08:50.710 --> 02:08:53.153 They we were unable to find that

NOTE Confidence: 0.730639867142857

02:08:53.153 --> 02:08:55.288 it was superior to be on both.

NOTE Confidence: 0.850112674666667

02:08:57.340 --> 02:08:58.840 And again, this is what

NOTE Confidence: 0.850112674666667

02:08:58.840 --> 02:09:00.040 I had mentioned before.

NOTE Confidence: 0.850112674666667

02:09:00.040 --> 02:09:03.990 The 57% composite outcome versus

NOTE Confidence: 0.850112674666667

02:09:03.990 --> 02:09:07.124 the 40% kidney composite outcome.

NOTE Confidence: 0.850112674666667

02:09:07.124 --> 02:09:10.054 And again there are more

NOTE Confidence: 0.850112674666667

02:09:10.054 --> 02:09:12.658 people in this lower group,

NOTE Confidence: 0.850112674666667

02:09:12.660 --> 02:09:14.018 so I'm going to focus on that.

NOTE Confidence: 0.850112674666667

02:09:14.020 --> 02:09:15.640 But basically if you were

NOTE Confidence: 0.850112674666667

02:09:15.640 --> 02:09:17.260 not an SGLT 2 inhibitor,

NOTE Confidence: 0.850112674666667

02:09:17.260 --> 02:09:19.868 you did well and and really you cannot

NOTE Confidence: 0.850112674666667

02:09:19.868 --> 02:09:22.219 really tell that this one and this

NOTE Confidence: 0.850112674666667

02:09:22.219 --> 02:09:24.310 one are different from each other.

NOTE Confidence: 0.759999501428571

02:09:26.850 --> 02:09:29.244 And so more importantly, is it safe?

NOTE Confidence: 0.759999501428571

02:09:29.250 --> 02:09:31.402 Because that's also important.

NOTE Confidence: 0.759999501428571

02:09:31.402 --> 02:09:34.630 And looking at any adverse events,

NOTE Confidence: 0.759999501428571

02:09:34.630 --> 02:09:37.262 those that were on SGLT 2 inhibitor

NOTE Confidence: 0.759999501428571

02:09:37.262 --> 02:09:40.286 versus not an SGLT 2 inhibitor had

NOTE Confidence: 0.759999501428571

02:09:40.286 --> 02:09:43.004 about similar number of adverse events

NOTE Confidence: 0.759999501428571

02:09:43.010 --> 02:09:45.360 and significantly those that were

NOTE Confidence: 0.759999501428571

02:09:45.360 --> 02:09:48.317 an SGLT 2 inhibitor and finerenone

NOTE Confidence: 0.759999501428571

02:09:48.317 --> 02:09:51.957 perhaps had even a lower levels of

NOTE Confidence: 0.759999501428571

02:09:51.957 --> 02:09:54.727 hyperkalemia than those that were not.

NOTE Confidence: 0.759999501428571

02:09:54.730 --> 02:09:56.956 So you can compare the 14 versus.

NOTE Confidence: 0.759999501428571

02:09:56.960 --> 02:10:00.117 And and the placebo was seven versus

NOTE Confidence: 0.759999501428571

02:10:00.120 --> 02:10:03.558 2.7 so so that's quite important,

NOTE Confidence: 0.759999501428571

02:10:03.560 --> 02:10:05.870 because we obviously do not want

NOTE Confidence: 0.759999501428571

02:10:05.870 --> 02:10:08.330 to provide a medication that will

NOTE Confidence: 0.759999501428571

02:10:08.330 --> 02:10:10.980 have a more serious adverse events.

NOTE Confidence: 0.759999501428571

02:10:10.980 --> 02:10:12.105 So in summary,

NOTE Confidence: 0.759999501428571

02:10:12.105 --> 02:10:13.980 the patients treated with an

NOTE Confidence: 0.759999501428571

02:10:13.980 --> 02:10:16.481 SGLT 2 inhibitor at baseline had

NOTE Confidence: 0.759999501428571

02:10:16.481 --> 02:10:18.566 higher mean E GFR lower.

NOTE Confidence: 0.759999501428571

02:10:18.570 --> 02:10:20.789 You're now going into creatinine ratio and

NOTE Confidence: 0.759999501428571

02:10:20.789 --> 02:10:23.079 how you're use of statins and GLP one,

NOTE Confidence: 0.759999501428571

02:10:23.080 --> 02:10:25.504 but there was a consistent kidney

NOTE Confidence: 0.759999501428571

02:10:25.504 --> 02:10:26.716 and cardiovascular benefit

NOTE Confidence: 0.759999501428571

02:10:26.716 --> 02:10:28.800 from finerenone versus placebo.

NOTE Confidence: 0.759999501428571

02:10:28.800 --> 02:10:31.959 Whether you were on SGLT 2 inhibitors or not,

NOTE Confidence: 0.759999501428571

02:10:31.960 --> 02:10:35.187 and it looked like the safety outcomes

NOTE Confidence: 0.759999501428571

02:10:35.187 --> 02:10:37.336 were consistent irrespective of whether

NOTE Confidence: 0.759999501428571

02:10:37.336 --> 02:10:39.744 you used SGLT 2 inhibitors or not.

NOTE Confidence: 0.759999501428571

02:10:39.750 --> 02:10:41.750 And so we need obviously.

NOTE Confidence: 0.759999501428571

02:10:41.750 --> 02:10:46.047 Now the more people use SGLT 2 inhibitors,

NOTE Confidence: 0.759999501428571

02:10:46.050 --> 02:10:48.858 but it would be a fantastic to do a

NOTE Confidence: 0.759999501428571

02:10:48.858 --> 02:10:51.815 study where we can do maybe a factor

NOTE Confidence: 0.759999501428571

02:10:51.815 --> 02:10:54.589 design or combine them with or without,

NOTE Confidence: 0.759999501428571

02:10:54.590 --> 02:10:56.872 et cetera to really see if there

NOTE Confidence: 0.759999501428571

02:10:56.872 --> 02:10:58.490 is a combined benefit.

NOTE Confidence: 0.911432057272727

02:11:01.170 --> 02:11:02.502 Next I was going to discuss

NOTE Confidence: 0.911432057272727

02:11:02.502 --> 02:11:03.710 as many of you know,

NOTE Confidence: 0.911432057272727

02:11:03.710 --> 02:11:05.525 I'm very interested in health

NOTE Confidence: 0.911432057272727

02:11:05.525 --> 02:11:08.332 disparities, and surprisingly,

NOTE Confidence: 0.911432057272727

02:11:08.332 --> 02:11:11.286 this will be the largest or this

NOTE Confidence: 0.911432057272727

02:11:11.286 --> 02:11:13.699 is the largest clinical trial

NOTE Confidence: 0.911432057272727

02:11:13.699 --> 02:11:15.650 that has Hispanic patients,

NOTE Confidence: 0.911432057272727

02:11:15.650 --> 02:11:19.010 so I thought it would be very

NOTE Confidence: 0.911432057272727

02:11:19.010 --> 02:11:21.855 important to look and see if there

NOTE Confidence: 0.911432057272727

02:11:21.855 --> 02:11:24.708 was any difference in outcomes between

NOTE Confidence: 0.911432057272727

02:11:24.708 --> 02:11:27.750 patients that were Hispanic or not,

NOTE Confidence: 0.911432057272727

02:11:27.750 --> 02:11:30.370 and so this is that trial.

NOTE Confidence: 0.911432057272727

02:11:30.370 --> 02:11:33.650 This was presented this year as an abstract

NOTE Confidence: 0.911432057272727

02:11:33.731 --> 02:11:37.083 in the NKS Spring clinical meeting in Boston.

NOTE Confidence: 0.911432057272727

02:11:37.090 --> 02:11:38.374 And as you know,

NOTE Confidence: 0.911432057272727

02:11:38.374 --> 02:11:40.950 Hispanics are more likely to have diabetes,

NOTE Confidence: 0.911432057272727

02:11:40.950 --> 02:11:42.415 and they're more likely to

NOTE Confidence: 0.911432057272727

02:11:42.415 --> 02:11:43.587 have chronic kidney disease.

NOTE Confidence: 0.911432057272727

02:11:43.590 --> 02:11:45.330 This is data from the CDC,

NOTE Confidence: 0.911432057272727

02:11:45.330 --> 02:11:47.766 the latest data, which is available,

NOTE Confidence: 0.911432057272727

02:11:47.770 --> 02:11:50.860 and you can see that they're more

NOTE Confidence: 0.911432057272727

02:11:50.860 --> 02:11:53.785 likely to have undiagnosed diabetes.

NOTE Confidence: 0.911432057272727

02:11:53.790 --> 02:11:56.310 So while it's in white,

NOTE Confidence: 0.911432057272727

02:11:56.310 --> 02:11:59.472 non Hispanic whites is about 2.7% and

NOTE Confidence: 0.911432057272727

02:11:59.472 --> 02:12:02.538 Hispanics is about four point 4%,

NOTE Confidence: 0.911432057272727

02:12:02.540 --> 02:12:05.370 so that's quite a difference.

NOTE Confidence: 0.911432057272727

02:12:05.370 --> 02:12:06.398 And Hispanics.

NOTE Confidence: 0.911432057272727

02:12:06.398 --> 02:12:07.940 As well as,

NOTE Confidence: 0.911432057272727

02:12:07.940 --> 02:12:09.460 African Americans are more

NOTE Confidence: 0.911432057272727

02:12:09.460 --> 02:12:10.600 likely to progress.

NOTE Confidence: 0.911432057272727

02:12:10.600 --> 02:12:12.410 This is Melissa data showing

NOTE Confidence: 0.911432057272727

02:12:12.410 --> 02:12:14.860 that in a short period of time,

NOTE Confidence: 0.911432057272727

02:12:14.860 --> 02:12:17.566 which was five years Black and

NOTE Confidence: 0.911432057272727

02:12:17.566 --> 02:12:19.831 Hispanics were more likely to

NOTE Confidence: 0.911432057272727

02:12:19.831 --> 02:12:22.708 progress to it's severe category

NOTE Confidence: 0.911432057272727

02:12:22.708 --> 02:12:27.078 of of chronic kidney disease.

NOTE Confidence: 0.911432057272727

02:12:27.080 --> 02:12:28.858 And you can see that over time,

NOTE Confidence: 0.911432057272727

02:12:28.860 --> 02:12:31.480 the incidence of diabetes related

NOTE Confidence: 0.911432057272727

02:12:31.480 --> 02:12:33.928 in stage renal disease has

NOTE Confidence: 0.911432057272727

02:12:33.928 --> 02:12:35.320 declined a little bit.

NOTE Confidence: 0.911432057272727

02:12:35.320 --> 02:12:38.029 If you look over the 20 years a little

NOTE Confidence: 0.911432057272727

02:12:38.029 --> 02:12:41.162 bit on in blacks a little bit in

NOTE Confidence: 0.911432057272727

02:12:41.162 --> 02:12:43.154 Hispanics significantly as we have

NOTE Confidence: 0.911432057272727

02:12:43.154 --> 02:12:45.356 what we know in Native Americans.

NOTE Confidence: 0.911432057272727

02:12:45.360 --> 02:12:46.326 But still,

NOTE Confidence: 0.911432057272727

02:12:46.326 --> 02:12:50.190 that rate is much higher than other groups.

NOTE Confidence: 0.911432057272727

02:12:50.190 --> 02:12:52.850 So like I told you,

NOTE Confidence: 0.911432057272727

02:12:52.850 --> 02:12:54.998 this is the largest clinical trial

NOTE Confidence: 0.911432057272727

02:12:54.998 --> 02:12:56.670 that involves Hispanics and it.

NOTE Confidence: 0.911432057272727

02:12:56.670 --> 02:12:58.480 Basically it's because it was

NOTE Confidence: 0.911432057272727

02:12:58.480 --> 02:12:59.566 an international trial.

NOTE Confidence: 0.911432057272727

02:12:59.570 --> 02:13:03.802 So a third of these 2100 were in the

NOTE Confidence: 0.911432057272727

02:13:03.802 --> 02:13:08.190 US and the others are from Mexico,

NOTE Confidence: 0.911432057272727

02:13:08.190 --> 02:13:09.514 Colombia, Brazil,

NOTE Confidence: 0.911432057272727

02:13:09.514 --> 02:13:13.486 where the study was also done.

NOTE Confidence: 0.911432057272727

02:13:13.490 --> 02:13:15.026 They're a little bit in Asia.

NOTE Confidence: 0.911432057272727

02:13:15.030 --> 02:13:16.884 I think there were five participants

NOTE Confidence: 0.911432057272727

02:13:16.884 --> 02:13:19.352 in Asia and like 30 or so in

NOTE Confidence: 0.911432057272727

02:13:19.352 --> 02:13:20.520 Europe that identified that.

NOTE Confidence: 0.911432057272727

02:13:20.520 --> 02:13:21.358 That's Hispanic,

NOTE Confidence: 0.911432057272727

02:13:21.358 --> 02:13:24.710 but you can see and this has been

NOTE Confidence: 0.911432057272727

02:13:24.801 --> 02:13:27.921 reported in by others and including

NOTE Confidence: 0.911432057272727

02:13:27.921 --> 02:13:31.053 ourselves that A1C control is worse

NOTE Confidence: 0.911432057272727

02:13:31.053 --> 02:13:33.945 in Hispanics and also very important,

NOTE Confidence: 0.911432057272727

02:13:33.950 --> 02:13:37.742 that they're less likely to be

NOTE Confidence: 0.911432057272727

02:13:37.742 --> 02:13:40.702 on medications to improve their

NOTE Confidence: 0.911432057272727

02:13:40.702 --> 02:13:41.764 diabetic control.

NOTE Confidence: 0.911432057272727

02:13:41.764 --> 02:13:43.357 Their glycemic control,

NOTE Confidence: 0.911432057272727

02:13:43.360 --> 02:13:45.979 so they were less likely to be on GLP.

NOTE Confidence: 0.911432057272727

02:13:45.980 --> 02:13:47.531 One receptor agonist,

NOTE Confidence: 0.911432057272727

02:13:47.531 --> 02:13:51.176 so 3.6 compared to 8, and they were less.

NOTE Confidence: 0.911432057272727

02:13:51.176 --> 02:13:53.520 Likely to be an SGLT 2 inhibitors,

NOTE Confidence: 0.911432057272727

02:13:53.520 --> 02:13:55.158 5% five point,

NOTE Confidence: 0.911432057272727

02:13:55.158 --> 02:13:58.690 1% versus 7% the rest of it is

NOTE Confidence: 0.911432057272727

02:13:58.690 --> 02:14:00.580 about what one would expect.

NOTE Confidence: 0.911432057272727

02:14:00.580 --> 02:14:02.180 The GFR is very similar.

NOTE Confidence: 0.911432057272727

02:14:02.180 --> 02:14:04.045 The year noblemen to creatinine

NOTE Confidence: 0.911432057272727

02:14:04.045 --> 02:14:06.230 ratio was very similar, etcetera.

NOTE Confidence: 0.70573477

02:14:08.980 --> 02:14:12.908 And so this is the very similar as

NOTE Confidence: 0.70573477

02:14:12.908 --> 02:14:16.073 what I showed you before the the top

NOTE Confidence: 0.70573477

02:14:16.073 --> 02:14:18.449 is cardiovascular composite outcome.

NOTE Confidence: 0.70573477

02:14:18.450 --> 02:14:20.796 The bottom is the kidney outcome.

NOTE Confidence: 0.70573477

02:14:20.800 --> 02:14:22.456 The blue section here,

NOTE Confidence: 0.70573477

02:14:22.456 --> 02:14:24.526 and is the Venera known.

NOTE Confidence: 0.70573477

02:14:24.530 --> 02:14:28.042 This is placebo and anything on this side

NOTE Confidence: 0.70573477

02:14:28.042 --> 02:14:31.048 favors funeral or anything less than one,

NOTE Confidence: 0.70573477

02:14:31.050 --> 02:14:33.000 and you can see that for

NOTE Confidence: 0.70573477

02:14:33.000 --> 02:14:33.975 the cardiovascular outcomes,

NOTE Confidence: 0.70573477

02:14:33.980 --> 02:14:35.186 and again similar,

NOTE Confidence: 0.70573477

02:14:35.186 --> 02:14:38.000 the Hispanic group is the smallest group.

NOTE Confidence: 0.70573477

02:14:38.000 --> 02:14:39.477 So obviously it's going to have the.

NOTE Confidence: 0.70573477

02:14:39.480 --> 02:14:40.174 Confident interval,

NOTE Confidence: 0.70573477

02:14:40.174 --> 02:14:42.603 but we can safely say that definitely

NOTE Confidence: 0.70573477

02:14:42.603 --> 02:14:44.600 for the cardiovascular outcomes.

NOTE Confidence: 0.70573477

02:14:44.600 --> 02:14:46.430 The outcomes are very similar

NOTE Confidence: 0.70573477

02:14:46.430 --> 02:14:48.644 and there was no interaction and

NOTE Confidence: 0.70573477

02:14:48.644 --> 02:14:50.249 for the kidney composite outcome

NOTE Confidence: 0.70573477

02:14:50.249 --> 02:14:52.512 I have to tell you that I saw

NOTE Confidence: 0.70573477

02:14:52.512 --> 02:14:55.970 the 69 this 6.5 versus 6.6.

NOTE Confidence: 0.70573477

02:14:55.970 --> 02:14:57.440 I was like oh I don't know,

NOTE Confidence: 0.70573477

02:14:57.440 --> 02:14:59.860 but it's statistically they're not,

NOTE Confidence: 0.70573477

02:14:59.860 --> 02:15:01.738 is significantly different and you can

NOTE Confidence: 0.70573477

02:15:01.738 --> 02:15:04.110 see that because the numbers are smaller.

NOTE Confidence: 0.70573477

02:15:04.110 --> 02:15:05.860 That's confidence intervals are wider,

NOTE Confidence: 0.70573477

02:15:05.860 --> 02:15:06.570 and again,

NOTE Confidence: 0.70573477

02:15:06.570 --> 02:15:09.055 the test for interaction was also negative.

NOTE Confidence: 0.646811821285714

02:15:11.580 --> 02:15:14.380 And it's very important to note and,

NOTE Confidence: 0.646811821285714

02:15:14.380 --> 02:15:17.166 and this is known that Hispanics again

NOTE Confidence: 0.646811821285714

02:15:17.166 --> 02:15:19.899 lose kidney function at a much higher

NOTE Confidence: 0.646811821285714

02:15:19.899 --> 02:15:21.734 rate than non Hispanic patients.

NOTE Confidence: 0.646811821285714

02:15:21.740 --> 02:15:24.392 So the while the difference is

NOTE Confidence: 0.646811821285714

02:15:24.392 --> 02:15:26.800 very similar between both groups,

NOTE Confidence: 0.646811821285714

02:15:26.800 --> 02:15:30.559 the Hispanics lost about 1.2 a year.

NOTE Confidence: 0.646811821285714

02:15:30.560 --> 02:15:33.456 Here this is one you can see that

NOTE Confidence: 0.646811821285714

02:15:33.456 --> 02:15:36.302 in reality they they were losing 4.5

NOTE Confidence: 0.646811821285714

02:15:36.302 --> 02:15:38.416 a year compared to the the plus.

NOTE Confidence: 0.646811821285714

02:15:38.420 --> 02:15:39.680 This is the finerenone group.

NOTE Confidence: 0.646811821285714

02:15:39.680 --> 02:15:41.376 This is the placebo group, finerenone.

NOTE Confidence: 0.646811821285714

02:15:41.376 --> 02:15:44.500 Placebo and you can see that there

NOTE Confidence: 0.646811821285714

02:15:44.500 --> 02:15:46.420 was a you know significant difference,

NOTE Confidence: 0.646811821285714

02:15:46.420 --> 02:15:49.801 but that 4.5 is very similar to

NOTE Confidence: 0.646811821285714

02:15:49.801 --> 02:15:51.580 what we have a.

NOTE Confidence: 0.646811821285714

02:15:51.580 --> 02:15:53.350 Published before this is data from

NOTE Confidence: 0.646811821285714

02:15:53.350 --> 02:15:55.354 the Jocelyn and you can see remember

NOTE Confidence: 0.646811821285714

02:15:55.354 --> 02:15:57.503 for this study you had to have severe

NOTE Confidence: 0.646811821285714

02:15:57.503 --> 02:15:59.554 albuminuria to be part of the study,

NOTE Confidence: 0.646811821285714

02:15:59.560 --> 02:16:01.680 so that's why if you look at it,

NOTE Confidence: 0.646811821285714

02:16:01.680 --> 02:16:03.858 we have published that they almost

NOTE Confidence: 0.646811821285714

02:16:03.858 --> 02:16:06.518 lose 5 amounts a year every year.

NOTE Confidence: 0.646811821285714

02:16:06.520 --> 02:16:08.000 If you have severe albuminuria,

NOTE Confidence: 0.646811821285714

02:16:08.000 --> 02:16:10.655 so that's very consistent with

NOTE Confidence: 0.646811821285714

02:16:10.655 --> 02:16:12.248 our finding too.

NOTE Confidence: 0.646811821285714

02:16:12.250 --> 02:16:14.420 And looking at adverse events

NOTE Confidence: 0.646811821285714

02:16:14.420 --> 02:16:16.156 which are quite important,

NOTE Confidence: 0.646811821285714

02:16:16.160 --> 02:16:18.624 if you can see that the Hispanic

NOTE Confidence: 0.646811821285714

02:16:18.624 --> 02:16:21.360 group had less adverse events and

NOTE Confidence: 0.646811821285714

02:16:21.360 --> 02:16:23.500 less outcomes for hyperkalemia.

NOTE Confidence: 0.838176400941176

02:16:25.520 --> 02:16:27.410 So in conclusion, the efficacy and

NOTE Confidence: 0.838176400941176

02:16:27.410 --> 02:16:29.445 safety of reneuron known observed in

NOTE Confidence: 0.838176400941176

02:16:29.445 --> 02:16:31.240 the overall population of Fidelity,

02:16:31.240 --> 02:16:34.502 did not have any difference between Hispanic

02:16:34.502 --> 02:16:37.784 and non Hispanic patients and the data

02:16:37.784 --> 02:16:40.490 support the use in Hispanic patients.

02:16:40.490 --> 02:16:44.288 I wanted to show now a case from the

02:16:44.288 --> 02:16:46.888 kidney Precision Medicine project and

02:16:46.888 --> 02:16:51.580 I I hope that you find it interesting.

02:16:51.580 --> 02:16:54.868 I am as I said before,

02:16:54.870 --> 02:16:56.820 I spend a significant amount of

02:16:56.820 --> 02:16:59.050 time within these two projects that

02:16:59.050 --> 02:17:00.770 which are collaborative projects

02:17:00.770 --> 02:17:02.943 in the kidney Precision Medicine

02:17:02.943 --> 02:17:04.888 project and the Apollo study.

02:17:04.890 --> 02:17:05.896 But again,

02:17:05.896 --> 02:17:09.920 we are in the data gathering phase and.

02:17:09.920 --> 02:17:11.504 I don't, I don't.

02:17:11.504 --> 02:17:14.320 I'm unable to represent more precise data,

NOTE Confidence: 0.838176400941176

02:17:14.320 --> 02:17:15.979 but this is the key PMP study.

NOTE Confidence: 0.838176400941176

02:17:15.980 --> 02:17:18.212 I know you're all familiar with

NOTE Confidence: 0.838176400941176

02:17:18.212 --> 02:17:20.418 it because Doctor Wilson is an

NOTE Confidence: 0.838176400941176

02:17:20.418 --> 02:17:22.368 investigator on the study and GAIL

NOTE Confidence: 0.838176400941176

02:17:22.368 --> 02:17:25.004 has been a Ki site at the jostling

NOTE Confidence: 0.838176400941176

02:17:25.004 --> 02:17:26.788 where a chronic kidney disease site.

NOTE Confidence: 0.838176400941176

02:17:26.788 --> 02:17:28.312 And obviously because we see a

NOTE Confidence: 0.838176400941176

02:17:28.312 --> 02:17:30.019 lot of patients with diabetes,

NOTE Confidence: 0.838176400941176

02:17:30.020 --> 02:17:32.045 we mostly recruit patients with

NOTE Confidence: 0.838176400941176

02:17:32.045 --> 02:17:34.070 diabetes and chronic kidney disease.

NOTE Confidence: 0.838176400941176

02:17:34.070 --> 02:17:38.061 And these are the sites and we recruit

NOTE Confidence: 0.838176400941176

02:17:38.061 --> 02:17:40.946 patients with diabetic kidney disease.

NOTE Confidence: 0.838176400941176

02:17:40.950 --> 02:17:43.550 Whether it be type one or type 2,

NOTE Confidence: 0.838176400941176

02:17:43.550 --> 02:17:47.288 chronic kidney disease or a proteinuria.

NOTE Confidence: 0.838176400941176

02:17:47.290 --> 02:17:49.030 And of the patients that we

02:17:49.030 --> 02:17:50.670 have recruited at the Joslin,

02:17:50.670 --> 02:17:53.106 which we have 33 patients so far

02:17:53.106 --> 02:17:55.509 and the study you know every

02:17:55.509 --> 02:17:57.639 time there's a COVID pandemic,

02:17:57.640 --> 02:17:59.696 we have to a COVID wave we have

02:17:59.696 --> 02:18:01.669 to stop recruitment etcetera.

02:18:01.670 --> 02:18:03.770 But we have obviously found

02:18:03.770 --> 02:18:05.870 mostly in diabetic kidney disease,

02:18:05.870 --> 02:18:11.720 but we've had four cases of the 23.

02:18:11.720 --> 02:18:14.294 21 are patients with diabetes and

02:18:14.294 --> 02:18:16.966 chronic kidney disease and four cases

02:18:16.966 --> 02:18:19.594 have been non diabetic kidney disease.

02:18:19.600 --> 02:18:22.824 So we have an average 19% of our

02:18:22.824 --> 02:18:25.152 patients that we think have diabetic

02:18:25.152 --> 02:18:27.386 kidney disease really don't have

02:18:27.386 --> 02:18:29.496 diabetic kidney disease and they

NOTE Confidence: 0.838176400941176

02:18:29.496 --> 02:18:31.768 have something else and so I think

NOTE Confidence: 0.838176400941176

02:18:31.768 --> 02:18:33.980 this this study for at least for

NOTE Confidence: 0.838176400941176

02:18:33.980 --> 02:18:36.314 me has highlighted that it perhaps

NOTE Confidence: 0.838176400941176

02:18:36.314 --> 02:18:39.180 biopsies should be more normal than

NOTE Confidence: 0.838176400941176

02:18:39.180 --> 02:18:42.300 the exception which I think was.

NOTE Confidence: 0.838176400941176

02:18:42.300 --> 02:18:45.884 They really are thought before in this group.

NOTE Confidence: 0.838176400941176

02:18:45.890 --> 02:18:47.835 The reason why the denominator

NOTE Confidence: 0.838176400941176

02:18:47.835 --> 02:18:50.874 was on 21 is because there's two

NOTE Confidence: 0.838176400941176

02:18:50.874 --> 02:18:52.906 patients that are resistors,

NOTE Confidence: 0.838176400941176

02:18:52.910 --> 02:18:54.885 so these are truly the

NOTE Confidence: 0.838176400941176

02:18:54.885 --> 02:18:56.070 most altruistic patients.

NOTE Confidence: 0.838176400941176

02:18:56.070 --> 02:18:58.065 These are patients that have type one

NOTE Confidence: 0.838176400941176

02:18:58.065 --> 02:19:00.270 diabetes and do not have kidney disease.

NOTE Confidence: 0.838176400941176

02:19:00.270 --> 02:19:02.218 They have normal GFR.

NOTE Confidence: 0.838176400941176

02:19:02.218 --> 02:19:04.166 They have no albuminuria,

02:19:04.170 --> 02:19:07.642 and they still volunteer to have a kidney

02:19:07.642 --> 02:19:10.900 biopsy so they can help us determine.

02:19:10.900 --> 02:19:12.575 You know what causes kidney

02:19:12.575 --> 02:19:14.250 disease in patients with diabetes?

02:19:16.260 --> 02:19:19.036 So this is a one of our cases,

02:19:19.040 --> 02:19:23.430 and as you can see here, this is.

02:19:23.430 --> 02:19:26.559 Just what we would normally call diabetic

02:19:26.559 --> 02:19:29.720 kidney disease or Miss Stangel expansion.

02:19:29.720 --> 02:19:31.160 But the tubules are OK.

02:19:31.160 --> 02:19:34.680 Perhaps some in beginnings of

02:19:34.680 --> 02:19:37.496 increased tubular basement membrane

02:19:37.500 --> 02:19:41.980 and we have the benefit at jostling

02:19:41.980 --> 02:19:45.380 that we're we're also doing it and

02:19:45.380 --> 02:19:47.500 ancillary study looking at retina.

02:19:47.500 --> 02:19:50.008 So this patient had her eyes

02:19:50.008 --> 02:19:52.220 had studies in her eyes,

NOTE Confidence: 0.9207781975

02:19:52.220 --> 02:19:55.700 and you can see all these dots are

NOTE Confidence: 0.9207781975

02:19:55.700 --> 02:20:00.668 really burns right from laser treatment.

NOTE Confidence: 0.9207781975

02:20:00.670 --> 02:20:02.896 Because she had diabetic retinopathy and you

NOTE Confidence: 0.9207781975

02:20:02.896 --> 02:20:05.700 can see here she has a little hemorrhage too.

NOTE Confidence: 0.9207781975

02:20:05.700 --> 02:20:07.012 That was her left.

NOTE Confidence: 0.9207781975

02:20:07.012 --> 02:20:08.980 That previous one was her right.

NOTE Confidence: 0.9207781975

02:20:08.980 --> 02:20:11.308 This is her left eye and

NOTE Confidence: 0.9207781975

02:20:11.308 --> 02:20:13.979 when we looked at her biopsy,

NOTE Confidence: 0.9207781975

02:20:13.980 --> 02:20:17.028 this is confocal analysis and you

NOTE Confidence: 0.9207781975

02:20:17.028 --> 02:20:21.510 can see her glomeruli in in green.

NOTE Confidence: 0.9207781975

02:20:21.510 --> 02:20:23.446 Right here.

NOTE Confidence: 0.9207781975

02:20:23.446 --> 02:20:29.539 And this is highlighted the medolla.

NOTE Confidence: 0.9207781975

02:20:29.540 --> 02:20:32.688 And here on the left, what showed up?

NOTE Confidence: 0.9207781975

02:20:32.688 --> 02:20:36.120 We have some kidneys that are

NOTE Confidence: 0.9207781975

02:20:36.120 --> 02:20:39.120 coming from nephrectomy for cancer,

NOTE Confidence: 0.9207781975

02:20:39.120 --> 02:20:40.684 or for other reasons,

NOTE Confidence: 0.9207781975

02:20:40.684 --> 02:20:43.615 and so this we we call it normal.

NOTE Confidence: 0.9207781975

02:20:43.615 --> 02:20:45.820 So this is supposed to be the

NOTE Confidence: 0.9207781975

02:20:45.820 --> 02:20:47.677 normal side of of that kidney,

NOTE Confidence: 0.9207781975

02:20:47.680 --> 02:20:51.360 and we it's used sort of to compare

NOTE Confidence: 0.9207781975

02:20:51.360 --> 02:20:54.490 our biopsies to sort of the normal.

NOTE Confidence: 0.9207781975

02:20:54.490 --> 02:20:57.381 And using this CD 31 staining which

NOTE Confidence: 0.9207781975

02:20:57.381 --> 02:21:00.169 is staining for endothelium cells,

NOTE Confidence: 0.9207781975

02:21:00.170 --> 02:21:02.186 you can see that in the normal,

NOTE Confidence: 0.9207781975

02:21:02.190 --> 02:21:08.454 then the glomeruli not quite small and very.

NOTE Confidence: 0.9207781975

02:21:08.460 --> 02:21:10.650 Him.

NOTE Confidence: 0.9207781975

02:21:10.650 --> 02:21:11.930 Like fixed in here,

NOTE Confidence: 0.9207781975

02:21:11.930 --> 02:21:14.610 you can see that our little glomeruli,

NOTE Confidence: 0.9207781975

02:21:14.610 --> 02:21:17.610 kind of hairy, and I'll show you bigger

NOTE Confidence: 0.9207781975

02:21:17.610 --> 02:21:19.979 picture and more fuzzy let's say.

NOTE Confidence: 0.9207781975

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02:21:19.980 --> 02:21:21.174 I don't know if that's the

NOTE Confidence: 0.9207781975

02:21:21.174 --> 02:21:22.456 scientific term for it, but anyway,

NOTE Confidence: 0.9207781975

02:21:22.456 --> 02:21:24.744 and you can see, here's the glomerella.

NOTE Confidence: 0.9207781975

02:21:24.744 --> 02:21:26.496 Here's the vascular poll.

NOTE Confidence: 0.9207781975

02:21:26.500 --> 02:21:29.636 And here are our glomeruli from our patient,

NOTE Confidence: 0.9207781975

02:21:29.640 --> 02:21:31.978 and you can see that the Vascular

NOTE Confidence: 0.9207781975

02:21:31.978 --> 02:21:34.170 poll is thickened compared to here,

NOTE Confidence: 0.9207781975

02:21:34.170 --> 02:21:36.480 and that it looks like there's

NOTE Confidence: 0.9207781975

02:21:36.480 --> 02:21:37.250 a communication.

NOTE Confidence: 0.9207781975

02:21:37.250 --> 02:21:38.474 You can see it a little bit here,

NOTE Confidence: 0.9207781975

02:21:38.480 --> 02:21:41.152 better with the CD 31 that I'll have

NOTE Confidence: 0.9207781975

02:21:41.152 --> 02:21:43.492 all these hairs of blood vessels

NOTE Confidence: 0.9207781975

02:21:43.492 --> 02:21:46.330 coming and talking to each other here.

NOTE Confidence: 0.9207781975

02:21:46.330 --> 02:21:49.610 And and that for us was a surprise.

NOTE Confidence: 0.9207781975

02:21:49.610 --> 02:21:52.474 Remember I I just talked told you that

NOTE Confidence: 0.9207781975

02:21:52.474 --> 02:21:55.689 we need as a group to discuss the case,

NOTE Confidence: 0.9207781975

02:21:55.690 --> 02:21:58.594 cases and sometimes we're lucky that

NOTE Confidence: 0.9207781975

02:21:58.594 --> 02:22:00.964 the tissue interrogation side have

NOTE Confidence: 0.9207781975

02:22:00.964 --> 02:22:03.118 processed the the the tissue and

NOTE Confidence: 0.9207781975

02:22:03.118 --> 02:22:05.957 are able to add to our discussions.

NOTE Confidence: 0.9207781975

02:22:05.960 --> 02:22:08.672 And that's how we were discussing

NOTE Confidence: 0.9207781975

02:22:08.672 --> 02:22:11.041 this case because of against her

NOTE Confidence: 0.9207781975

02:22:11.041 --> 02:22:12.726 participation in the retina study.

NOTE Confidence: 0.9207781975

02:22:12.730 --> 02:22:15.634 And here are some more images of these,

NOTE Confidence: 0.9207781975

02:22:15.640 --> 02:22:16.496 you know.

NOTE Confidence: 0.9207781975

02:22:16.496 --> 02:22:18.636 Cherry like structures that turned

NOTE Confidence: 0.9207781975

02:22:18.636 --> 02:22:21.844 out to be endothelium coming out

NOTE Confidence: 0.9207781975

02:22:21.844 --> 02:22:23.290 of the glomerulus.

NOTE Confidence: 0.9207781975

02:22:23.290 --> 02:22:23.682 And.

NOTE Confidence: 0.9207781975

02:22:23.682 --> 02:22:26.426 So here you can see again a

NOTE Confidence: 0.9207781975

02:22:26.426 --> 02:22:29.038 depiction of the Bowmans capsule,

NOTE Confidence: 0.9207781975

02:22:29.040 --> 02:22:32.955 and here again the the blood vessels

NOTE Confidence: 0.9207781975

02:22:32.955 --> 02:22:35.770 that are outside the Bowman capsule.

NOTE Confidence: 0.9207781975

02:22:35.770 --> 02:22:40.546 And to me that was new and surprising,

NOTE Confidence: 0.9207781975

02:22:40.550 --> 02:22:43.486 but so we went back to the biopsy.

NOTE Confidence: 0.9207781975

02:22:43.490 --> 02:22:45.070 And so we started looking.

NOTE Confidence: 0.9207781975

02:22:45.070 --> 02:22:47.331 And then once once you see the

NOTE Confidence: 0.9207781975

02:22:47.331 --> 02:22:49.510 other one then you can easily

NOTE Confidence: 0.9207781975

02:22:49.510 --> 02:22:51.026 recognize it here too.

NOTE Confidence: 0.9207781975

02:22:51.030 --> 02:22:53.415 So these are endothelial cells

NOTE Confidence: 0.9207781975

02:22:53.415 --> 02:22:55.800 that we're seeing in the

NOTE Confidence: 0.870040819166667

02:22:55.889 --> 02:22:57.189 other staining,

NOTE Confidence: 0.870040819166667

02:22:57.190 --> 02:22:59.948 and you can see that here too.

NOTE Confidence: 0.870040819166667

02:22:59.950 --> 02:23:03.370 Again, here's the Vascular poll thickness

NOTE Confidence: 0.870040819166667

02:23:03.370 --> 02:23:08.236 and again more endothelial cells here.

NOTE Confidence: 0.870040819166667

02:23:08.240 --> 02:23:10.907 And also here in this sort of

NOTE Confidence: 0.870040819166667

02:23:10.907 --> 02:23:13.955 Broken Arrow you can see that even

NOTE Confidence: 0.870040819166667

02:23:13.955 --> 02:23:16.230 in the endothelial cells there's

NOTE Confidence: 0.870040819166667

02:23:16.230 --> 02:23:18.760 this increase based on membrane.

NOTE Confidence: 0.870040819166667

02:23:18.760 --> 02:23:21.400 And again this is all endothelium

NOTE Confidence: 0.870040819166667

02:23:21.400 --> 02:23:23.962 and all the glomeruli had this

NOTE Confidence: 0.870040819166667

02:23:23.962 --> 02:23:26.640 sort of structure in this biopsy.

NOTE Confidence: 0.870040819166667

02:23:26.640 --> 02:23:29.259 And so of course we thought this was new

NOTE Confidence: 0.870040819166667

02:23:29.259 --> 02:23:31.933 and then we found out that it's not so.

NOTE Confidence: 0.870040819166667

02:23:31.940 --> 02:23:34.813 It turns out that this investigator

NOTE Confidence: 0.870040819166667

02:23:34.813 --> 02:23:38.731 1985 published in the Archives of

NOTE Confidence: 0.870040819166667

02:23:38.731 --> 02:23:42.687 Histology in Japan that he looked at

NOTE Confidence: 0.870040819166667

02:23:42.687 --> 02:23:46.069 3000 glomeruli using a what I assume

NOTE Confidence: 0.870040819166667

02:23:46.069 --> 02:23:48.874 at the time was novel technology

NOTE Confidence: 0.870040819166667

02:23:48.874 --> 02:23:51.459 which was electron microscopy and

NOTE Confidence: 0.870040819166667

02:23:51.459 --> 02:23:54.700 he created this vascular cast and

NOTE Confidence: 0.870040819166667

02:23:54.700 --> 02:23:56.848 then he painstakingly counted.

NOTE Confidence: 0.870040819166667

02:23:56.850 --> 02:23:58.438 In the 3000 glomeruli,

NOTE Confidence: 0.870040819166667

02:23:58.438 --> 02:24:00.820 how many blood vessels came in

NOTE Confidence: 0.870040819166667

02:24:00.897 --> 02:24:03.069 and out of the blood vessels?

NOTE Confidence: 0.870040819166667

02:24:03.070 --> 02:24:04.630 I show you a picture.

NOTE Confidence: 0.870040819166667

02:24:04.630 --> 02:24:06.166 This is one of this picture.

NOTE Confidence: 0.870040819166667

02:24:06.170 --> 02:24:09.290 So this is the single a ferrant arterial,

NOTE Confidence: 0.870040819166667

02:24:09.290 --> 02:24:12.466 and then this is again he only found

NOTE Confidence: 0.870040819166667

02:24:12.466 --> 02:24:15.366 two in this nephrectomy that he had.

NOTE Confidence: 0.870040819166667

02:24:15.370 --> 02:24:16.990 He found two glomeruli,

NOTE Confidence: 0.870040819166667

02:24:16.990 --> 02:24:19.705 one with five blood, eferin blood vessels,

NOTE Confidence: 0.870040819166667

02:24:19.705 --> 02:24:21.165 and one with three.

NOTE Confidence: 0.870040819166667

02:24:21.170 --> 02:24:22.750 Both pictures are here,

NOTE Confidence: 0.870040819166667

02:24:22.750 --> 02:24:25.120 but I only presented the one

NOTE Confidence: 0.870040819166667

02:24:25.201 --> 02:24:26.878 with the 5E ferrant arterials.

NOTE Confidence: 0.870040819166667

02:24:26.878 --> 02:24:30.259 And here he had to cut E5 and E4

NOTE Confidence: 0.870040819166667

02:24:30.259 --> 02:24:32.269 are cut because otherwise you

NOTE Confidence: 0.870040819166667

02:24:32.269 --> 02:24:35.498 couldn't see the other ones, he said.

NOTE Confidence: 0.870040819166667

02:24:35.498 --> 02:24:36.052 And.

NOTE Confidence: 0.870040819166667

02:24:36.052 --> 02:24:39.930 And then what we weren't sure is,

NOTE Confidence: 0.870040819166667

02:24:39.930 --> 02:24:42.040 had this been described in

NOTE Confidence: 0.870040819166667

02:24:42.040 --> 02:24:43.728 diabetic kidney disease and

NOTE Confidence: 0.870040819166667

02:24:43.728 --> 02:24:45.950 then we found this one again,

NOTE Confidence: 0.870040819166667

02:24:45.950 --> 02:24:49.730 another investigator again in the

NOTE Confidence: 0.870040819166667

02:24:49.730 --> 02:24:55.980 80s that also said that one to 5% of

NOTE Confidence: 0.870040819166667

02:24:55.980 --> 02:24:59.610 the glomeruli in this diabetes and

NOTE Confidence: 0.870040819166667

02:24:59.610 --> 02:25:03.727 kidney that he saw in 12 individuals

NOTE Confidence: 0.870040819166667

02:25:03.730 --> 02:25:08.240 and have this capillary profiles.

NOTE Confidence: 0.870040819166667

02:25:08.240 --> 02:25:11.552 We called it outside the glomerella

NOTE Confidence: 0.870040819166667

02:25:11.552 --> 02:25:15.487 tough and to be honest we had four

NOTE Confidence: 0.870040819166667

02:25:15.487 --> 02:25:18.616 or five pathologists in in our group

NOTE Confidence: 0.870040819166667

02:25:18.616 --> 02:25:22.402 and it it seemed like this didn't

NOTE Confidence: 0.870040819166667

02:25:22.402 --> 02:25:25.197 really move outside this journal,

NOTE Confidence: 0.870040819166667

02:25:25.200 --> 02:25:26.610 which now forget what it's called.

NOTE Confidence: 0.870040819166667

02:25:26.610 --> 02:25:28.825 Journal of diabetic complications because

NOTE Confidence: 0.870040819166667

02:25:28.825 --> 02:25:32.038 it was also news and to the group.

NOTE Confidence: 0.870040819166667

02:25:32.040 --> 02:25:35.127 So now we're going back and looking

NOTE Confidence: 0.870040819166667

02:25:35.127 --> 02:25:38.202 at all our other diabetic biopsies.

NOTE Confidence: 0.870040819166667

02:25:38.202 --> 02:25:40.618 To see if we have the same finding.

NOTE Confidence: 0.870040819166667

02:25:40.620 --> 02:25:42.642 Because right now we actually don't

NOTE Confidence: 0.870040819166667

02:25:42.642 --> 02:25:45.189 know if this is important or not,

NOTE Confidence: 0.870040819166667

02:25:45.190 --> 02:25:49.590 or is this significant in any way clinically?

NOTE Confidence: 0.870040819166667

02:25:49.590 --> 02:25:52.847 Because other than that we have not it.

NOTE Confidence: 0.870040819166667

02:25:52.847 --> 02:25:53.618 We're looking still,

NOTE Confidence: 0.870040819166667

02:25:53.618 --> 02:25:54.646 and through the literature,

NOTE Confidence: 0.870040819166667

02:25:54.650 --> 02:25:57.009 but we haven't found anything that has

NOTE Confidence: 0.870040819166667

02:25:57.009 --> 02:25:59.484 looked at what disease hairy glomeruli

NOTE Confidence: 0.870040819166667

02:25:59.484 --> 02:26:02.346 really mean clinically for the patient,

230

02:26:02.350 --> 02:26:05.380 so I thought I would give

02:26:05.380 --> 02:26:08.320 this sort of little.

02:26:08.320 --> 02:26:11.428 Shout out to KPMP and thank you

02:26:11.428 --> 02:26:14.239 for your support of the project.

02:26:14.240 --> 02:26:16.848 This is I want to thank all of

02:26:16.848 --> 02:26:18.738 the individuals that are involved

02:26:18.738 --> 02:26:20.449 in the fidelity trials.

02:26:20.449 --> 02:26:24.761 And and this is the conclusion I let

02:26:24.761 --> 02:26:29.006 you read that I also wanted to thank

02:26:29.010 --> 02:26:31.810 my collaborators and all my other projects,

02:26:31.810 --> 02:26:35.790 my staff and my colleagues,

02:26:35.790 --> 02:26:38.640 and the funders obviously of

02:26:38.640 --> 02:26:41.490 the projects for their support,

02:26:41.490 --> 02:26:45.030 and I'm happy to stop sharing.

02:26:45.030 --> 02:26:47.240 If you have any questions.

02:26:57.520 --> 02:26:58.880 Thanks for a great talk,

NOTE Confidence: 0.738110112

02:26:58.880 --> 02:27:01.600 Sylvia. Any questions Jeff.

NOTE Confidence: 0.75177572

02:27:03.670 --> 02:27:06.370 Just a question about Panera.

NOTE Confidence: 0.75177572

02:27:06.370 --> 02:27:09.317 There were no type 1 diabetics in.

NOTE Confidence: 0.75177572

02:27:09.320 --> 02:27:10.376 Infidelity or Figaro,

NOTE Confidence: 0.75177572

02:27:10.376 --> 02:27:12.488 and that's not the the non

NOTE Confidence: 0.75177572

02:27:12.488 --> 02:27:14.390 diabetic pilot starting is there.

NOTE Confidence: 0.75177572

02:27:14.390 --> 02:27:16.846 Is there any concern or reason why it

NOTE Confidence: 0.75177572

02:27:16.846 --> 02:27:19.527 would be beneficial in that population?

NOTE Confidence: 0.75177572

02:27:19.530 --> 02:27:22.716 OK so I I have to repeat the question

NOTE Confidence: 0.75177572

02:27:22.716 --> 02:27:25.461 so the question is that there

NOTE Confidence: 0.75177572

02:27:25.461 --> 02:27:28.842 were no type one patients in the

NOTE Confidence: 0.75177572

02:27:28.842 --> 02:27:31.307 Fidelio trials or Figaro trials,

NOTE Confidence: 0.75177572

02:27:31.310 --> 02:27:33.790 and if there is any concern of using

NOTE Confidence: 0.75177572

02:27:33.790 --> 02:27:35.589 finerenone in type one patients,

NOTE Confidence: 0.75177572

02:27:35.590 --> 02:27:38.590 is that the question?

NOTE Confidence: 0.75177572

02:27:38.590 --> 02:27:40.534 Right, so you're correct.

NOTE Confidence: 0.75177572

02:27:40.534 --> 02:27:42.964 So right now these medications

NOTE Confidence: 0.75177572

02:27:42.964 --> 02:27:46.134 are approved for patients with or.

NOTE Confidence: 0.75177572

02:27:46.134 --> 02:27:48.816 The studies were done in patients

NOTE Confidence: 0.75177572

02:27:48.816 --> 02:27:51.848 with type 2 diabetes and a I.

NOTE Confidence: 0.75177572

02:27:51.848 --> 02:27:54.224 I don't see why you couldn't

NOTE Confidence: 0.75177572

02:27:54.224 --> 02:27:56.358 use them in type one,

NOTE Confidence: 0.75177572

02:27:56.360 --> 02:27:57.921 and actually now that you said that

NOTE Confidence: 0.75177572

02:27:57.921 --> 02:27:59.496 I'm going to read out the label

NOTE Confidence: 0.75177572

02:27:59.496 --> 02:28:01.465 because I don't know if the label says

NOTE Confidence: 0.75177572

02:28:01.465 --> 02:28:03.060 chronic kidney disease with diabetes,

NOTE Confidence: 0.75177572

02:28:03.060 --> 02:28:05.160 or does it specifically say type two?

NOTE Confidence: 0.75177572

02:28:05.160 --> 02:28:07.068 I would have to guess that

NOTE Confidence: 0.75177572

02:28:07.068 --> 02:28:08.530 it specifically says Type 2.

NOTE Confidence: 0.75177572

02:28:08.530 --> 02:28:11.610 But once the medication is FDA approved,

NOTE Confidence: 0.75177572

02:28:11.610 --> 02:28:12.750 it can be used.

NOTE Confidence: 0.75177572

02:28:12.750 --> 02:28:13.890 I guess off label,

NOTE Confidence: 0.75177572

02:28:13.890 --> 02:28:18.012 but I I don't see why it wouldn't work.

NOTE Confidence: 0.75177572

02:28:18.020 --> 02:28:20.852 I mean it doesn't alter any

NOTE Confidence: 0.75177572

02:28:20.852 --> 02:28:21.640 glycemic pathways.

NOTE Confidence: 0.75177572

02:28:21.640 --> 02:28:24.120 Kind of like SGLT 2 that was done

NOTE Confidence: 0.75177572

02:28:24.120 --> 02:28:26.572 in in type twos and the the reason

NOTE Confidence: 0.75177572

02:28:26.572 --> 02:28:29.320 we don't use them in type ones is

NOTE Confidence: 0.75177572

02:28:29.320 --> 02:28:31.627 because they're already prone to DKA,

NOTE Confidence: 0.75177572

02:28:31.627 --> 02:28:35.763 and we don't want to give them another

NOTE Confidence: 0.75177572

02:28:35.763 --> 02:28:38.799 medication that it will do harm, right?

NOTE Confidence: 0.75177572

02:28:38.799 --> 02:28:39.617 That will.

NOTE Confidence: 0.75177572

02:28:39.617 --> 02:28:42.480 Increase the risk of a serious complication,

NOTE Confidence: 0.75177572

02:28:42.480 --> 02:28:44.940 so, but it's a good question.

NOTE Confidence: 0.75177572

02:28:44.940 --> 02:28:46.128 I would say right now they're

NOTE Confidence: 0.75177572

02:28:46.128 --> 02:28:46.920 approved for Type 2,

NOTE Confidence: 0.75177572

02:28:46.920 --> 02:28:48.963 but I don't see why it couldn't be used.

NOTE Confidence: 0.949355616666667

02:28:55.430 --> 02:28:56.558 Any other questions?

NOTE Confidence: 0.62396264

02:28:58.640 --> 02:29:01.060 It. So Sylvia.

NOTE Confidence: 0.20090899

02:29:05.120 --> 02:29:07.510 More. OK.

NOTE Confidence: 0.47424413875

02:29:10.990 --> 02:29:13.718 So the group of Mount Sinai has decided.

NOTE Confidence: 0.4398898

02:29:21.040 --> 02:29:25.390 To distinguish this city from Janet.

NOTE Confidence: 0.16118315

02:29:28.450 --> 02:29:28.980 I.

NOTE Confidence: 0.785689187777778

02:29:31.470 --> 02:29:33.927 Doctor Shiva can you repeat that question

NOTE Confidence: 0.785689187777778

02:29:33.927 --> 02:29:37.039 because I I heard something about my

NOTE Confidence: 0.785689187777778

02:29:37.039 --> 02:29:39.027 Sinai and distinguishing ethnicity,

NOTE Confidence: 0.785689187777778

02:29:39.030 --> 02:29:40.700 but I can't hear it, sorry.

NOTE Confidence: 0.808509414166667

02:29:43.340 --> 02:29:45.412 Genetic ancestry versus ethnicity.

NOTE Confidence: 0.808509414166667

02:29:45.412 --> 02:29:48.954 So I think at Mount Sinai they

NOTE Confidence: 0.808509414166667

02:29:48.954 --> 02:29:50.640 had stated that they might be

NOTE Confidence: 0.808509414166667

02:29:50.640 --> 02:29:51.980 able to tell the difference,

NOTE Confidence: 0.808509414166667

02:29:51.980 --> 02:29:53.527 and are you able to tell the

NOTE Confidence: 0.808509414166667

02:29:53.527 --> 02:29:54.530 difference in your study?

NOTE Confidence: 0.6799378995

02:29:56.740 --> 02:30:01.045 And so, in in Hispanics, no.

NOTE Confidence: 0.6799378995

02:30:01.045 --> 02:30:05.140 We you know, as a Hispanic myself,

NOTE Confidence: 0.6799378995

02:30:05.140 --> 02:30:06.622 I can tell you that before

NOTE Confidence: 0.6799378995

02:30:06.622 --> 02:30:08.160 I came to this country,

NOTE Confidence: 0.6799378995

02:30:08.160 --> 02:30:11.216 I had never heard that we were different.

NOTE Confidence: 0.6799378995

02:30:11.220 --> 02:30:13.350 So I think it's like something

NOTE Confidence: 0.6799378995

02:30:13.350 --> 02:30:15.838 that when you cross the US border,

NOTE Confidence: 0.6799378995

02:30:15.840 --> 02:30:18.528 you're no longer Colombian like I'm

NOTE Confidence: 0.6799378995

02:30:18.528 --> 02:30:20.320 from Colombia background you're

NOTE Confidence: 0.6799378995

02:30:20.390 --> 02:30:24.350 now Hispanic, but in Colombia.

NOTE Confidence: 0.6799378995

02:30:24.350 --> 02:30:29.230 We know that we're a mix of different people.

NOTE Confidence: 0.875163685454545

02:30:31.300 --> 02:30:33.799 So I don't know that we don't

NOTE Confidence: 0.875163685454545

02:30:33.799 --> 02:30:35.350 have that distinguished there.

NOTE Confidence: 0.808749158461539

02:30:37.580 --> 02:30:41.156 So I I we only know where the

02:30:41.156 --> 02:30:43.578 the country of origin is.

02:30:43.580 --> 02:30:44.644 And like I said,

02:30:44.644 --> 02:30:46.700 most of the patients were from Mexico,

02:30:46.700 --> 02:30:48.878 Colombia, Brazil and the United States.

02:30:48.880 --> 02:30:50.360 That's that we do know,

02:30:50.360 --> 02:30:52.820 and we did look by country.

02:30:52.820 --> 02:30:54.945 If there were any differences

02:30:54.945 --> 02:30:57.104 in results that we do do,

02:30:57.104 --> 02:30:59.060 and in fact we were particularly

02:30:59.137 --> 02:31:00.805 interested because they have

02:31:00.805 --> 02:31:03.307 less adverse events and we were

02:31:03.379 --> 02:31:05.923 wondering if is it because reporting

02:31:05.923 --> 02:31:08.426 was different by country and we

02:31:08.426 --> 02:31:10.038 looked particularly by that.

02:31:10.040 --> 02:31:12.866 And that was the same everywhere.

02:31:12.870 --> 02:31:17.740 And. But that's it there.

NOTE Confidence: 0.808749158461539

02:31:17.740 --> 02:31:19.628 That's all the information I have about that.

NOTE Confidence: 0.889313892

02:31:23.480 --> 02:31:25.600 Alright, there's no other questions.

NOTE Confidence: 0.889313892

02:31:25.600 --> 02:31:26.636 Thank you very much.

NOTE Confidence: 0.889313892

02:31:26.636 --> 02:31:28.190 Doctor Roses for our wonderful talk.

NOTE Confidence: 0.75252142

02:31:40.640 --> 02:31:42.352 I docked emberg alright,

NOTE Confidence: 0.75252142

02:31:42.352 --> 02:31:44.920 so I'll introduce the next speaker.

NOTE Confidence: 0.75252142

02:31:44.920 --> 02:31:48.220 Are you able to share your? Let me just.

NOTE Confidence: 0.867325116666667

02:32:01.700 --> 02:32:03.740 OK, are you seeing my slides?

NOTE Confidence: 0.867325116666667

02:32:03.740 --> 02:32:05.918 That looks great.

NOTE Confidence: 0.867325116666667

02:32:05.920 --> 02:32:08.362 So like to introduce saw Doctor

NOTE Confidence: 0.867325116666667

02:32:08.362 --> 02:32:10.624 Denberg from the Children's Hospital

NOTE Confidence: 0.867325116666667

02:32:10.624 --> 02:32:12.860 of Philadelphia Permanent School

NOTE Confidence: 0.867325116666667

02:32:12.860 --> 02:32:15.655 Medicine at University of Pennsylvania,

NOTE Confidence: 0.867325116666667

02:32:15.660 --> 02:32:17.560 and she'll discuss the epidemiology

NOTE Confidence: 0.867325116666667

02:32:17.560 --> 02:32:19.460 of kidney stone disease from

NOTE Confidence: 0.867325116666667

02:32:19.524 --> 02:32:21.009 origins to complications.

NOTE Confidence: 0.93303324125

02:32:23.110 --> 02:32:26.134 Thank you for the opportunity to speak today.

NOTE Confidence: 0.8808399

02:32:29.610 --> 02:32:32.210 These are my disclosures,

NOTE Confidence: 0.8808399

02:32:32.210 --> 02:32:33.870 not relevant to what I'm

NOTE Confidence: 0.8808399

02:32:33.870 --> 02:32:35.530 going to talk about today.

NOTE Confidence: 0.8808399

02:32:35.530 --> 02:32:37.238 Except the NIH funding.

NOTE Confidence: 0.837377261411765

02:32:39.650 --> 02:32:42.810 So by way of an outline I'm going to 1st

NOTE Confidence: 0.837377261411765

02:32:42.897 --> 02:32:46.460 talk about some of the changing epidemiology.

NOTE Confidence: 0.837377261411765

02:32:46.460 --> 02:32:48.938 In terms of incidence of kidney stone

NOTE Confidence: 0.837377261411765

02:32:48.938 --> 02:32:51.607 disease and and that the impact of that

NOTE Confidence: 0.837377261411765

02:32:51.610 --> 02:32:55.526 when we talk about origins of kidney stone

NOTE Confidence: 0.837377261411765

02:32:55.526 --> 02:32:57.705 disease focusing on emerging evidence

NOTE Confidence: 0.837377261411765

02:32:57.705 --> 02:33:01.010 for the role of the gut kidney access,

NOTE Confidence: 0.837377261411765

02:33:01.010 --> 02:33:04.106 and then I want to touch on complications,

NOTE Confidence: 0.837377261411765

02:33:04.110 --> 02:33:06.840 particularly in terms of kidney bone

NOTE Confidence: 0.837377261411765

02:33:06.840 --> 02:33:09.230 vascular access and in making this talk,

NOTE Confidence: 0.837377261411765

02:33:09.230 --> 02:33:11.680 I've tried to highlight key themes that

NOTE Confidence: 0.837377261411765

02:33:11.680 --> 02:33:14.208 have been central to my research program,

NOTE Confidence: 0.837377261411765

02:33:14.210 --> 02:33:15.932 so the work that I'm going to

NOTE Confidence: 0.837377261411765

02:33:15.932 --> 02:33:16.670 talk about integrates.

NOTE Confidence: 0.837377261411765

02:33:16.670 --> 02:33:19.780 Epidemiology and patient oriented research,

NOTE Confidence: 0.837377261411765

02:33:19.780 --> 02:33:22.060 including analysis of large electronic

NOTE Confidence: 0.837377261411765

02:33:22.060 --> 02:33:24.340 health record and claims data,

NOTE Confidence: 0.837377261411765

02:33:24.340 --> 02:33:26.305 as well as observational and

NOTE Confidence: 0.837377261411765

02:33:26.305 --> 02:33:27.877 translational patient oriented studies,

NOTE Confidence: 0.837377261411765

02:33:27.880 --> 02:33:30.100 and we've really tried to approach

NOTE Confidence: 0.837377261411765

02:33:30.100 --> 02:33:31.580 questions and evidence gaps

NOTE Confidence: 0.837377261411765

02:33:31.640 --> 02:33:33.490 from a life course perspective.

NOTE Confidence: 0.858440193846154

02:33:37.130 --> 02:33:39.202 So we know that kidney stones result

NOTE Confidence: 0.858440193846154

02:33:39.202 --> 02:33:41.409 from a disorder of minimum metabolism,

NOTE Confidence: 0.858440193846154

02:33:41.410 --> 02:33:43.156 the risk of which is determined

NOTE Confidence: 0.858440193846154

02:33:43.156 --> 02:33:44.870 by the interaction of genetics,

NOTE Confidence: 0.858440193846154

02:33:44.870 --> 02:33:47.758 diet, and environmental exposures.

NOTE Confidence: 0.858440193846154

02:33:47.760 --> 02:33:49.878 The prevalence of kidney stones has

NOTE Confidence: 0.858440193846154

02:33:49.878 --> 02:33:52.510 increased 70% over the last three decades.

NOTE Confidence: 0.858440193846154

02:33:52.510 --> 02:33:54.658 And kidney stones are increasingly common

NOTE Confidence: 0.858440193846154

02:33:54.658 --> 02:33:56.914 with an estimated prevalence of 1 and

NOTE Confidence: 0.858440193846154

02:33:56.914 --> 02:33:58.450 11 individuals in the United States.

NOTE Confidence: 0.858440193846154

02:33:58.450 --> 02:34:02.468 So comparable to the prevalence of diabetes.

NOTE Confidence: 0.858440193846154

02:34:02.470 --> 02:34:04.220 Total annual charges exceed $10

NOTE Confidence: 0.858440193846154

02:34:04.220 --> 02:34:06.451 billion and that does not account

NOTE Confidence: 0.858440193846154

02:34:06.451 --> 02:34:08.546 for medication or indirect costs.

NOTE Confidence: 0.846186342

02:34:12.030 --> 02:34:14.070 In terms of stone composition,

NOTE Confidence: 0.846186342

02:34:14.070 --> 02:34:16.140 calcium oxalate stones remain the

NOTE Confidence: 0.846186342

02:34:16.140 --> 02:34:18.850 most common type of stone overall.

NOTE Confidence: 0.846186342

02:34:18.850 --> 02:34:20.930 Although hydroxy apatite stones were

NOTE Confidence: 0.846186342

02:34:20.930 --> 02:34:23.778 the second most common for each 555

NOTE Confidence: 0.846186342

02:34:23.778 --> 02:34:26.844 in this analysis and in this study,

NOTE Confidence: 0.846186342

02:34:26.850 --> 02:34:28.815 women submitted more stones than

NOTE Confidence: 0.846186342

02:34:28.815 --> 02:34:31.299 men between the ages of 10 and

NOTE Confidence: 0.846186342

02:34:31.299 --> 02:34:33.578 19 and 20 to 29 years of age.

NOTE Confidence: 0.902314795714286

02:34:36.990 --> 02:34:38.822 This leads to one of the main points

NOTE Confidence: 0.902314795714286

02:34:38.822 --> 02:34:40.348 I wanted to talk about today,

NOTE Confidence: 0.902314795714286

02:34:40.350 --> 02:34:42.252 which is the rising incidence of

NOTE Confidence: 0.902314795714286

02:34:42.252 --> 02:34:43.906 kidney stones, particularly in

NOTE Confidence: 0.902314795714286

02:34:43.906 --> 02:34:46.446 younger individuals and among women.

NOTE Confidence: 0.902314795714286

02:34:46.450 --> 02:34:48.680 So several studies have shown

NOTE Confidence: 0.902314795714286

02:34:48.680 --> 02:34:50.018 this disproportionate rise,

NOTE Confidence: 0.902314795714286

02:34:50.020 --> 02:34:52.029 and this is data from our population

NOTE Confidence: 0.902314795714286

02:34:52.029 --> 02:34:53.762 based study of temporal trends

NOTE Confidence: 0.902314795714286

02:34:53.762 --> 02:34:55.378 and kidney stone incidents.

NOTE Confidence: 0.902314795714286

02:34:55.380 --> 02:34:59.174 From 1997 to 2012 in South Carolina,

NOTE Confidence: 0.902314795714286

02:34:59.180 --> 02:35:01.154 you could see the cumulative risk of

NOTE Confidence: 0.902314795714286

02:35:01.154 --> 02:35:02.687 kidney stones doubled during childhood

NOTE Confidence: 0.902314795714286

02:35:02.687 --> 02:35:04.583 and the greatest increase in incidence

NOTE Confidence: 0.902314795714286

02:35:04.583 --> 02:35:06.490 was found among 15 to 19 year olds.

NOTE Confidence: 0.902314795714286

02:35:06.490 --> 02:35:10.706 With the 26% increased risk for five years.

NOTE Confidence: 0.902314795714286

02:35:10.710 --> 02:35:12.603 In multivariable analysis,

NOTE Confidence: 0.902314795714286

02:35:12.603 --> 02:35:15.127 it incidents increased 15%

NOTE Confidence: 0.902314795714286

02:35:15.130 --> 02:35:16.550 per five years among females,

NOTE Confidence: 0.902314795714286

02:35:16.550 --> 02:35:18.230 but remains stable for males,

NOTE Confidence: 0.902314795714286

02:35:18.230 --> 02:35:20.318 resulting in a 45% increase in

NOTE Confidence: 0.902314795714286

02:35:20.318 --> 02:35:22.571 the lifetime risk of kidney stones

NOTE Confidence: 0.902314795714286

02:35:22.571 --> 02:35:24.929 for women over the study period.

NOTE Confidence: 0.902314795714286

02:35:24.930 --> 02:35:25.466 And importantly,

NOTE Confidence: 0.902314795714286

02:35:25.466 --> 02:35:27.342 this shift in kidney stones to a

NOTE Confidence: 0.902314795714286

02:35:27.342 --> 02:35:29.429 younger age of onset has caused

NOTE Confidence: 0.902314795714286

02:35:29.429 --> 02:35:30.488 increasing hospitalization surgeries

NOTE Confidence: 0.902314795714286

02:35:30.488 --> 02:35:31.860 and healthcare expenditures.

NOTE Confidence: 0.903299123846154

02:35:35.930 --> 02:35:38.084 Also reflecting the more severe phenotype

NOTE Confidence: 0.903299123846154

02:35:38.084 --> 02:35:40.808 of a disease that starts in childhood,

NOTE Confidence: 0.903299123846154

02:35:40.810 --> 02:35:43.170 the probability of a symptomatic

NOTE Confidence: 0.903299123846154

02:35:43.170 --> 02:35:46.003 recurrence within three years of the

NOTE Confidence: 0.903299123846154

02:35:46.003 --> 02:35:48.740 index stone and childhood is about 50%.

NOTE Confidence: 0.903299123846154

02:35:48.740 --> 02:35:50.910 Also, reflecting the rapid shift in the

NOTE Confidence: 0.903299123846154

02:35:50.910 --> 02:35:52.600 epidemiology of kidney stone disease,

NOTE Confidence: 0.903299123846154

02:35:52.600 --> 02:35:54.373 our knowledge base of how to reduce the risk

NOTE Confidence: 0.903299123846154

02:35:54.373 --> 02:35:56.210 of this recurrence remains quite limited.

NOTE Confidence: 0.909669316

02:36:00.900 --> 02:36:03.186 So one of the key questions I'm going to

NOTE Confidence: 0.909669316

02:36:03.186 --> 02:36:05.486 spend some time talking about is the why,

NOTE Confidence: 0.909669316

02:36:05.486 --> 02:36:07.397 why are we starting to form stones

NOTE Confidence: 0.909669316

02:36:07.397 --> 02:36:08.980 kidney stones earlier in life?

NOTE Confidence: 0.803083111

02:36:12.830 --> 02:36:15.755 So this brings me to the gut kidney access

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NOTE Confidence: 0.803083111

02:36:15.755 --> 02:36:18.136 and kidney stone disease discovering

NOTE Confidence: 0.803083111

02:36:18.136 --> 02:36:20.611 the causes of the epidemiologic

NOTE Confidence: 0.803083111

02:36:20.611 --> 02:36:23.020 shift in kidney stone disease could

NOTE Confidence: 0.803083111

02:36:23.020 --> 02:36:24.548 reveal new therapeutic targets,

NOTE Confidence: 0.803083111

02:36:24.550 --> 02:36:27.252 and the rapidity of the change in

NOTE Confidence: 0.803083111

02:36:27.252 --> 02:36:29.312 epidemiology suggests that the driving

NOTE Confidence: 0.803083111

02:36:29.312 --> 02:36:31.402 forces are external exposures such

NOTE Confidence: 0.803083111

02:36:31.402 --> 02:36:33.689 as dietary factors or medications,

NOTE Confidence: 0.803083111

02:36:33.690 --> 02:36:34.504 namely antibiotics.

NOTE Confidence: 0.803083111

02:36:34.504 --> 02:36:36.539 When we're thinking about disruption

NOTE Confidence: 0.803083111

02:36:36.539 --> 02:36:38.490 of the gut microbiome,

NOTE Confidence: 0.803083111

02:36:38.490 --> 02:36:40.010 so many of these exposures

NOTE Confidence: 0.803083111

02:36:40.010 --> 02:36:41.226 could impact the gut.

NOTE Confidence: 0.803083111

02:36:41.230 --> 02:36:41.930 Many access,

NOTE Confidence: 0.803083111

02:36:41.930 --> 02:36:43.680 which is that complex interplay

NOTE Confidence: 0.803083111

02:36:43.680 --> 02:36:45.404 between the intestinal and urinary

NOTE Confidence: 0.803083111

02:36:45.404 --> 02:36:47.246 tracts in human health and disease.

NOTE Confidence: 0.86000298

02:36:51.210 --> 02:36:53.044 So the first thing I want to

NOTE Confidence: 0.86000298

02:36:53.044 --> 02:36:55.010 show is from a study we did,

NOTE Confidence: 0.86000298

02:36:55.010 --> 02:36:57.320 it was designed to examine the association

NOTE Confidence: 0.86000298

02:36:57.320 --> 02:36:58.970 between oral antibiotic exposure

NOTE Confidence: 0.86000298

02:36:58.970 --> 02:37:01.070 and incident kidney stone disease.

NOTE Confidence: 0.86000298

02:37:01.070 --> 02:37:02.702 We sought to assess the strength

NOTE Confidence: 0.86000298

02:37:02.702 --> 02:37:04.151 and temporality of the association

NOTE Confidence: 0.86000298

02:37:04.151 --> 02:37:06.328 by antibiotic class and to test the

NOTE Confidence: 0.86000298

02:37:06.328 --> 02:37:07.983 hypothesis that earlier life exposure

NOTE Confidence: 0.86000298

02:37:07.983 --> 02:37:09.939 to oral antibiotics would be associated

NOTE Confidence: 0.86000298

02:37:09.939 --> 02:37:11.938 with the greater risk of kidney stones.

NOTE Confidence: 0.83406055

02:37:15.970 --> 02:37:18.959 We conducted this study in the health

NOTE Confidence: 0.83406055

02:37:18.959 --> 02:37:21.812 Improvement Network database and this was a

NOTE Confidence: 0.83406055

02:37:21.812 --> 02:37:24.062 population based nested case control study.

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NOTE Confidence: 0.83406055

02:37:24.070 --> 02:37:26.950 The Health improvement network within

NOTE Confidence: 0.83406055

02:37:26.950 --> 02:37:29.278 database is representative of the

NOTE Confidence: 0.83406055

02:37:29.278 --> 02:37:31.861 United Kingdom population by age, sex,

NOTE Confidence: 0.83406055

02:37:31.861 --> 02:37:33.816 medical conditions and mortality rates,

NOTE Confidence: 0.83406055

02:37:33.820 --> 02:37:36.365 and contains patient level electronic

NOTE Confidence: 0.83406055

02:37:36.365 --> 02:37:39.445 health record data for more than

NOTE Confidence: 0.83406055

02:37:39.445 --> 02:37:41.715 13 individuals among over 600

NOTE Confidence: 0.83406055

02:37:41.715 --> 02:37:44.240 practices in the United Kingdom.

NOTE Confidence: 0.83406055

02:37:44.240 --> 02:37:45.885 This database has been used to characterize

NOTE Confidence: 0.83406055

02:37:45.885 --> 02:37:47.160 outcomes and kidney stone disease.

NOTE Confidence: 0.83406055

02:37:47.160 --> 02:37:49.560 I'll show you some data later as well

NOTE Confidence: 0.83406055

02:37:49.560 --> 02:37:52.044 as the association between antibiotic

NOTE Confidence: 0.83406055

02:37:52.044 --> 02:37:55.069 exposure and inflammatory bowel disease.

NOTE Confidence: 0.83406055

02:37:55.070 --> 02:37:55.901 In this study,

NOTE Confidence: 0.83406055

02:37:55.901 --> 02:37:58.069 we looked at nearly 26,000 individuals who

NOTE Confidence: 0.83406055

02:37:58.069 --> 02:38:00.964 had instant kidney stone disease and to be

NOTE Confidence: 0.83406055

02:38:00.964 --> 02:38:03.160 considered a patient with incident stones,

NOTE Confidence: 0.83406055

02:38:03.160 --> 02:38:05.038 an individual had to be registered

NOTE Confidence: 0.83406055

02:38:05.038 --> 02:38:06.555 with their general practice for

NOTE Confidence: 0.83406055

02:38:06.555 --> 02:38:08.251 at least six months at the time of

NOTE Confidence: 0.83406055

02:38:08.251 --> 02:38:09.928 the initial qualified diagnosis.

NOTE Confidence: 0.83406055

02:38:09.930 --> 02:38:11.250 Code for kidney stones,

NOTE Confidence: 0.83406055

02:38:11.250 --> 02:38:13.230 and this has been a validated

NOTE Confidence: 0.83406055

02:38:13.301 --> 02:38:15.129 approach for ascertainment of

NOTE Confidence: 0.83406055

02:38:15.129 --> 02:38:17.414 incident diagnosis in this database.

NOTE Confidence: 0.83406055

02:38:17.420 --> 02:38:18.854 To increase precision,

NOTE Confidence: 0.83406055

02:38:18.854 --> 02:38:21.244 we included 10 controls for

NOTE Confidence: 0.83406055

02:38:21.244 --> 02:38:23.478 each case matched on age,

NOTE Confidence: 0.83406055

02:38:23.480 --> 02:38:23.846 sex,

NOTE Confidence: 0.83406055

02:38:23.846 --> 02:38:26.042 and general practice to each case

NOTE Confidence: 0.83406055

02:38:26.042 --> 02:38:28.080 that their index date of their

NOTE Confidence: 0.83406055

02:38:28.080 --> 02:38:29.600 first of their kidney stone.

NOTE Confidence: 0.92622917

02:38:34.040 --> 02:38:37.960 So this is the main output of this paper.

NOTE Confidence: 0.92622917

02:38:37.960 --> 02:38:39.880 It's a busy table,

NOTE Confidence: 0.92622917

02:38:39.880 --> 02:38:43.824 so each column represents a series of models.

NOTE Confidence: 0.92622917

02:38:43.830 --> 02:38:45.864 And what we found is that exposure

NOTE Confidence: 0.92622917

02:38:45.864 --> 02:38:48.108 to five classes of oral antibiotics,

NOTE Confidence: 0.92622917

02:38:48.110 --> 02:38:49.254 sulfa cephalosporins,

NOTE Confidence: 0.92622917

02:38:49.254 --> 02:38:50.398 fluoroquinolones nitrofurantoin,

NOTE Confidence: 0.92622917

02:38:50.398 --> 02:38:53.258 methenamine and broad spectrum penicillins

NOTE Confidence: 0.92622917

02:38:53.258 --> 02:38:55.820 were associated with increased odds of

NOTE Confidence: 0.92622917

02:38:55.820 --> 02:38:57.630 instant kidney stone disease within

NOTE Confidence: 0.92622917

02:38:57.630 --> 02:38:59.450 a 3 to 12 month exposure window,

NOTE Confidence: 0.92622917

02:38:59.450 --> 02:39:01.290 which was our primary exposure

NOTE Confidence: 0.92622917

02:39:01.290 --> 02:39:02.762 window for this analysis.

NOTE Confidence: 0.92622917

02:39:02.770 --> 02:39:05.038 And all of these models were adjusted

NOTE Confidence: 0.92622917

02:39:05.038 --> 02:39:07.279 for for numerous comorbid conditions.

NOTE Confidence: 0.92622917

02:39:07.280 --> 02:39:09.662 Urinary tract infection within the same

NOTE Confidence: 0.92622917

02:39:09.662 --> 02:39:12.030 exposure window and exposure to other

NOTE Confidence: 0.92622917

02:39:12.030 --> 02:39:13.454 potential confounding medications as

NOTE Confidence: 0.92622917

02:39:13.454 --> 02:39:16.350 well as rate of healthcare and counters.

NOTE Confidence: 0.92622917

02:39:16.350 --> 02:39:18.688 The models in column A made no

NOTE Confidence: 0.92622917

02:39:18.688 --> 02:39:20.749 adjustment for other antibiotic use.

NOTE Confidence: 0.78934965

02:39:22.790 --> 02:39:25.107 The models in column B adjusted for

NOTE Confidence: 0.78934965

02:39:25.107 --> 02:39:27.133 any other antibiotic use within the

NOTE Confidence: 0.78934965

02:39:27.133 --> 02:39:29.065 three to 12 month exposure window.

NOTE Confidence: 0.78934965

02:39:29.070 --> 02:39:30.658 And it model C.

NOTE Confidence: 0.78934965

02:39:30.658 --> 02:39:33.040 Each model was adjusted for every

NOTE Confidence: 0.78934965

02:39:33.122 --> 02:39:35.712 other antibiotic as 11 separate

NOTE Confidence: 0.78934965

02:39:35.712 --> 02:39:38.302 indicator variables in the model

NOTE Confidence: 0.78934965

02:39:38.390 --> 02:39:40.735 and Model C had the best fit.

NOTE Confidence: 0.78934965

02:39:40.740 --> 02:39:42.692 So the take home was that these 5

NOTE Confidence: 0.78934965

02:39:42.692 --> 02:39:44.030 broad spectrum antibiotic classes

NOTE Confidence: 0.78934965

02:39:44.030 --> 02:39:45.227 were independently associated

NOTE Confidence: 0.78934965

02:39:45.227 --> 02:39:47.920 with a 1.3 to 2.3 fold increase.

NOTE Confidence: 0.78934965

02:39:47.920 --> 02:39:50.152 The odds of kidney stones at a bumper

NOTE Confidence: 0.78934965

02:39:50.152 --> 02:39:52.030 only adjusted significance threshold.

NOTE Confidence: 0.7940064199

02:39:56.110 --> 02:39:57.412 An exploratory analysis,

NOTE Confidence: 0.7940064199

02:39:57.412 --> 02:40:00.016 we also looked for effect modification

NOTE Confidence: 0.7940064199

02:40:00.016 --> 02:40:03.201 by age and you can see here that we

NOTE Confidence: 0.7940064199

02:40:03.201 --> 02:40:05.232 found interactions with age for for

NOTE Confidence: 0.7940064199

02:40:05.232 --> 02:40:07.164 all 5 classes and abilities that

NOTE Confidence: 0.7940064199

02:40:07.170 --> 02:40:09.462 were significantly associated with

NOTE Confidence: 0.7940064199

02:40:09.462 --> 02:40:12.102 kidney stones on the prior slide.

NOTE Confidence: 0.7940064199

02:40:12.102 --> 02:40:14.340 So the odds of incident kidney

NOTE Confidence: 0.7940064199

02:40:14.419 --> 02:40:16.989 stones were greater for earlier

NOTE Confidence: 0.7940064199

02:40:16.989 --> 02:40:19.045 life exposures to antibiotics.

NOTE Confidence: 0.7940064199

02:40:19.050 --> 02:40:20.682 An exponential increase in the odds

NOTE Confidence: 0.7940064199

02:40:20.682 --> 02:40:22.355 of kidney stones was estimated for

NOTE Confidence: 0.7940064199

02:40:22.355 --> 02:40:24.210 patients less than 20 years of age,

NOTE Confidence: 0.7940064199

02:40:24.210 --> 02:40:26.345 exposed to self a drugs and broad

NOTE Confidence: 0.7940064199

02:40:26.345 --> 02:40:27.901 spectrum penicillins and a more

NOTE Confidence: 0.7940064199

02:40:27.901 --> 02:40:29.371 linear relationship was seen across

NOTE Confidence: 0.7940064199

02:40:29.371 --> 02:40:31.309 the age range for cephalosporins,

NOTE Confidence: 0.7940064199

02:40:31.310 --> 02:40:33.149 fluoroquinolones and nitrofurantoin.

NOTE Confidence: 0.857743494375

02:40:37.690 --> 02:40:40.354 We also examined the magnitude of

NOTE Confidence: 0.857743494375

02:40:40.354 --> 02:40:42.724 the association based on proximity

NOTE Confidence: 0.857743494375

02:40:42.724 --> 02:40:45.279 of exposure to Orlando Vedics.

NOTE Confidence: 0.857743494375

02:40:45.280 --> 02:40:47.302 This figure highlights that the odds

NOTE Confidence: 0.857743494375

02:40:47.302 --> 02:40:49.323 were greatest for exposure to the

NOTE Confidence: 0.857743494375

02:40:49.323 --> 02:40:50.873 five antibiotic classes of interest

NOTE Confidence: 0.857743494375

02:40:50.873 --> 02:40:52.907 within three to six months of the

NOTE Confidence: 0.857743494375

02:40:52.907 --> 02:40:54.479 index date of the kidney stone.

NOTE Confidence: 0.857743494375

02:40:54.480 --> 02:40:56.142 The magnitude of the increased ads

NOTE Confidence: 0.857743494375

02:40:56.142 --> 02:40:58.180 was lower with more distant exposure,

NOTE Confidence: 0.857743494375

02:40:58.180 --> 02:40:59.460 but remains statistically significant

NOTE Confidence: 0.857743494375

02:40:59.460 --> 02:41:01.751 from three to five years from exposure

NOTE Confidence: 0.857743494375

02:41:01.751 --> 02:41:03.635 for all classes except Buzz Spectrum,

NOTE Confidence: 0.857743494375

02:41:03.640 --> 02:41:04.912 penicillins, and again,

NOTE Confidence: 0.857743494375

02:41:04.912 --> 02:41:07.032 all of these conditional logistic

NOTE Confidence: 0.857743494375

02:41:07.032 --> 02:41:08.847 regression models were adjusted

NOTE Confidence: 0.857743494375

02:41:08.847 --> 02:41:10.655 for prevalent comorbid conditions.

NOTE Confidence: 0.857743494375

02:41:10.660 --> 02:41:13.606 UTI within the exposure window and

NOTE Confidence: 0.857743494375

02:41:13.606 --> 02:41:15.900 exposure to other potential confounding

NOTE Confidence: 0.857743494375

02:41:15.900 --> 02:41:17.950 medications within the exposure window.

NOTE Confidence: 0.858482602

02:41:21.380 --> 02:41:22.680 So to summarize this study,

NOTE Confidence: 0.858482602

02:41:22.680 --> 02:41:24.934 we found that exposure to broad spectrum

NOTE Confidence: 0.858482602

02:41:24.934 --> 02:41:26.754 oral antibiotics were associated increased

NOTE Confidence: 0.858482602

02:41:26.754 --> 02:41:28.754 odds of developing kidney stones,

NOTE Confidence: 0.858482602

02:41:28.760 --> 02:41:30.880 and that there appear to be greater risk

NOTE Confidence: 0.858482602

02:41:30.880 --> 02:41:33.197 for more recent and early life exposures.

NOTE Confidence: 0.858482602

02:41:33.200 --> 02:41:35.980 This data provides additional rationale,

NOTE Confidence: 0.858482602

02:41:35.980 --> 02:41:38.015 rationale to limit inappropriate antibiotic

NOTE Confidence: 0.858482602

02:41:38.015 --> 02:41:40.728 prescribing and may help explain some of

NOTE Confidence: 0.858482602

02:41:40.728 --> 02:41:42.576 the rising incidents of kidney stones,

NOTE Confidence: 0.858482602

02:41:42.580 --> 02:41:43.849 particularly among children.

NOTE Confidence: 0.79609846175

02:41:46.600 --> 02:41:48.415 To highlight that this slide

NOTE Confidence: 0.79609846175

02:41:48.415 --> 02:41:49.867 shows antibiotic prescribing and

NOTE Confidence: 0.79609846175

02:41:49.867 --> 02:41:51.411 this is actually data that's

NOTE Confidence: 0.79609846175

02:41:51.411 --> 02:41:53.091 a decade old at this point.

NOTE Confidence: 0.79609846175

02:41:53.100 --> 02:41:54.738 But antibiotic prescribing

NOTE Confidence: 0.79609846175

02:41:54.738 --> 02:41:57.468 for 1000 persons by state.

NOTE Confidence: 0.79609846175

02:41:57.470 --> 02:42:00.270 And so, in 2011 there were over

NOTE Confidence: 0.79609846175

02:42:00.270 --> 02:42:01.820 260 million courses of antibiotics

NOTE Confidence: 0.79609846175

02:42:01.820 --> 02:42:03.678 prescribed with the highest rates of

NOTE Confidence: 0.79609846175

02:42:03.678 --> 02:42:04.718 prescription for children younger

NOTE Confidence: 0.79609846175

02:42:04.718 --> 02:42:06.520 than 10 years of age and women.

NOTE Confidence: 0.812732084117647

02:42:10.860 --> 02:42:12.087 Corroborating our findings,

NOTE Confidence: 0.812732084117647

02:42:12.087 --> 02:42:14.541 this study of over 5000 women

NOTE Confidence: 0.812732084117647

02:42:14.541 --> 02:42:16.818 in the nurses health studies one

NOTE Confidence: 0.812732084117647

02:42:16.818 --> 02:42:18.980 and two showed that the use of

NOTE Confidence: 0.812732084117647

02:42:18.980 --> 02:42:20.809 antibiotics for more than two months

NOTE Confidence: 0.812732084117647

02:42:20.809 --> 02:42:22.801 in early adulthood and middle age

NOTE Confidence: 0.812732084117647

02:42:22.801 --> 02:42:24.688 was associated with a higher risk

NOTE Confidence: 0.812732084117647

02:42:24.688 --> 02:42:26.350 of kidney stones later in life.

NOTE Confidence: 0.812732084117647

02:42:26.350 --> 02:42:27.910 These are the adjusted hazard

NOTE Confidence: 0.812732084117647

02:42:27.910 --> 02:42:29.812 ratios from cause specific heads or

NOTE Confidence: 0.812732084117647

02:42:29.812 --> 02:42:31.540 regression that was adjusted for age,

NOTE Confidence: 0.812732084117647

02:42:31.540 --> 02:42:33.750 body mass index, comorbid conditions,

NOTE Confidence: 0.812732084117647

02:42:33.750 --> 02:42:36.170 thiazide use, and dietary factors,

NOTE Confidence: 0.812732084117647

02:42:36.170 --> 02:42:39.130 and importantly, this study.

NOTE Confidence: 0.812732084117647

02:42:39.130 --> 02:42:41.512 Actually was able to do medical

NOTE Confidence: 0.812732084117647

02:42:41.512 --> 02:42:44.826 record review to to confirm the stone

NOTE Confidence: 0.812732084117647

02:42:44.826 --> 02:42:47.370 composition and 80% of the subset of

NOTE Confidence: 0.812732084117647

02:42:47.370 --> 02:42:48.720 stones that were confirmed by this

NOTE Confidence: 0.812732084117647

02:42:48.770 --> 02:42:50.540 review were composed of calcium oxalate.

NOTE Confidence: 0.857556686

02:42:54.230 --> 02:42:56.750 So what's mediating this association?

NOTE Confidence: 0.857556686

02:42:56.750 --> 02:43:00.246 Well, we know that we are 10% human,

NOTE Confidence: 0.857556686

02:43:00.246 --> 02:43:03.054 and we cohabit with 100 trillion

NOTE Confidence: 0.857556686

02:43:03.054 --> 02:43:05.967 microbes that make up our microbiome,

NOTE Confidence: 0.857556686

02:43:05.970 --> 02:43:07.618 particularly inhabiting our mouth,

NOTE Confidence: 0.857556686

02:43:07.618 --> 02:43:10.340 skin, and intestine.

NOTE Confidence: 0.857556686

02:43:10.340 --> 02:43:12.332 And we know that this community

NOTE Confidence: 0.857556686

02:43:12.332 --> 02:43:14.150 is really essential for health.

NOTE Confidence: 0.860318715

02:43:18.570 --> 02:43:22.426 So this is a figure from an article

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NOTE Confidence: 0.860318715

02:43:22.426 --> 02:43:25.722 written by Doctor Blazer just highlighting

NOTE Confidence: 0.860318715

02:43:25.722 --> 02:43:29.220 the loss of biodiversity over time.

NOTE Confidence: 0.860318715

02:43:29.220 --> 02:43:31.704 And highlighting in the United States

NOTE Confidence: 0.860318715

02:43:31.704 --> 02:43:34.420 how this has happened simultaneously

NOTE Confidence: 0.860318715

02:43:34.420 --> 02:43:36.212 with early introduction of

NOTE Confidence: 0.860318715

02:43:36.212 --> 02:43:38.452 sanitation and early antibiotic use.

NOTE Confidence: 0.893314749285714

02:43:42.720 --> 02:43:45.366 There have been several studies that

NOTE Confidence: 0.893314749285714

02:43:45.366 --> 02:43:48.777 have begun to look at the microbial

NOTE Confidence: 0.893314749285714

02:43:48.777 --> 02:43:50.964 diversity of the intestinal microbiome

NOTE Confidence: 0.893314749285714

02:43:50.964 --> 02:43:53.044 in patients with kidney stones,

NOTE Confidence: 0.893314749285714

02:43:53.050 --> 02:43:56.356 so this is data from adult.

NOTE Confidence: 0.893314749285714

02:43:56.360 --> 02:43:58.164 Individuals who formed calcium

NOTE Confidence: 0.893314749285714

02:43:58.164 --> 02:44:00.419 based stones and had recurrent

NOTE Confidence: 0.893314749285714

02:44:00.419 --> 02:44:02.329 stones compared to controls.

NOTE Confidence: 0.893314749285714

02:44:02.330 --> 02:44:05.942 And you can see lower alpha

NOTE Confidence: 0.893314749285714

02:44:05.942 --> 02:44:07.794 diversity in the stone formers

NOTE Confidence: 0.893314749285714

02:44:07.794 --> 02:44:09.038 compared to healthy controls.

NOTE Confidence: 0.799633815

02:44:12.100 --> 02:44:15.150 In addition to demonstrating reduced

NOTE Confidence: 0.799633815

02:44:15.150 --> 02:44:18.200 diversity of the fecal microbiome,

NOTE Confidence: 0.799633815

02:44:18.200 --> 02:44:20.426 so some farmers also had lower

NOTE Confidence: 0.799633815

02:44:20.426 --> 02:44:21.910 representation of bacterial taxa

NOTE Confidence: 0.799633815

02:44:21.970 --> 02:44:24.370 predicted to be involved in Oxley

NOTE Confidence: 0.799633815

02:44:24.370 --> 02:44:26.455 degradation and reduced expression of

NOTE Confidence: 0.799633815

02:44:26.455 --> 02:44:28.555 genes belonging to oxalate degradation

NOTE Confidence: 0.799633815

02:44:28.555 --> 02:44:30.108 pathways and which shown here,

NOTE Confidence: 0.799633815

02:44:30.108 --> 02:44:31.800 is that the relative abundance of

NOTE Confidence: 0.799633815

02:44:31.854 --> 02:44:33.793 five tax that was also correlated with

NOTE Confidence: 0.799633815

02:44:33.793 --> 02:44:35.600 24 hour urinary oxalate excretion.

NOTE Confidence: 0.866191474

02:44:39.710 --> 02:44:42.304 This is data from a study that

NOTE Confidence: 0.866191474

02:44:42.304 --> 02:44:44.612 systematically reviewed six articles

NOTE Confidence: 0.866191474

02:44:44.612 --> 02:44:47.586 that was contained 170 adults with

NOTE Confidence: 0.866191474

02:44:47.586 --> 02:44:49.646 kidney stones showing lower abundance

NOTE Confidence: 0.866191474

02:44:49.646 --> 02:44:52.696 of several bacterial taxa as well as

NOTE Confidence: 0.866191474

02:44:52.696 --> 02:44:54.851 greater abundance of Bacteroides species.

NOTE Confidence: 0.828875238

02:44:58.290 --> 02:45:01.427 More recently, this meta analysis looked

NOTE Confidence: 0.828875238

02:45:01.427 --> 02:45:04.906 at 6 meta Genome Wide association studies.

NOTE Confidence: 0.828875238

02:45:04.910 --> 02:45:07.626 That evaluated the microbiome of the stool,

NOTE Confidence: 0.828875238

02:45:07.630 --> 02:45:09.070 and in some cases urine,

NOTE Confidence: 0.828875238

02:45:09.070 --> 02:45:12.849 as well as kidney stones themselves and

NOTE Confidence: 0.828875238

02:45:12.849 --> 02:45:15.401 the take home was that prevotella in the

NOTE Confidence: 0.828875238

02:45:15.401 --> 02:45:18.140 gut and lack the bacillus and urinary

NOTE Confidence: 0.828875238

02:45:18.140 --> 02:45:20.310 tract was associated with healthy.

NOTE Confidence: 0.828875238

02:45:20.310 --> 02:45:21.453 Individuals, while Enterobacteriaceae,

NOTE Confidence: 0.828875238

02:45:21.453 --> 02:45:23.739 were associated with kidney stone disease,

NOTE Confidence: 0.828875238

02:45:23.740 --> 02:45:25.540 both in the urine and in

NOTE Confidence: 0.828875238

02:45:25.540 --> 02:45:26.440 kidney stones themselves,

NOTE Confidence: 0.828875238

02:45:26.440 --> 02:45:28.330 and the predominant factors that

NOTE Confidence: 0.828875238

02:45:28.330 --> 02:45:29.842 were associated with microbiome

NOTE Confidence: 0.828875238

02:45:29.842 --> 02:45:31.519 composition were kidney stone status,

NOTE Confidence: 0.828875238

02:45:31.520 --> 02:45:33.089 stone composition, age,

NOTE Confidence: 0.828875238

02:45:33.089 --> 02:45:34.658 and study location.

NOTE Confidence: 0.8792779

02:45:37.280 --> 02:45:38.448 So what about children?

NOTE Confidence: 0.894390648636364

02:45:40.710 --> 02:45:43.095 So I'm going to share some of our work

NOTE Confidence: 0.894390648636364

02:45:43.095 --> 02:45:45.488 looking at the microbiome of children with

NOTE Confidence: 0.894390648636364

02:45:45.488 --> 02:45:47.739 kidney stones compared to healthy peers.

NOTE Confidence: 0.88337490625

02:45:50.510 --> 02:45:52.322 So this was a case control

NOTE Confidence: 0.88337490625

02:45:52.322 --> 02:45:54.463 study that we conducted at the

NOTE Confidence: 0.88337490625

02:45:54.463 --> 02:45:56.195 Children's Hospital of Philadelphia,

NOTE Confidence: 0.88337490625

02:45:56.200 --> 02:45:57.850 and we enrolled cases who were

NOTE Confidence: 0.88337490625

02:45:57.850 --> 02:46:00.011 between 4 and 18 years of age

NOTE Confidence: 0.88337490625

02:46:00.011 --> 02:46:01.347 with calcium kidney stones.

NOTE Confidence: 0.88337490625

02:46:01.350 --> 02:46:03.499 So they had to have had either

NOTE Confidence: 0.88337490625

02:46:03.499 --> 02:46:04.819 a spontaneously passed or

NOTE Confidence: 0.88337490625

02:46:04.819 --> 02:46:06.499 surgically removed stone that was

NOTE Confidence: 0.88337490625

02:46:06.499 --> 02:46:09.890 comprised of at least 80% calcium.

NOTE Confidence: 0.88337490625

02:46:09.890 --> 02:46:13.766 And 44 agent sex matched controls.

NOTE Confidence: 0.88337490625

02:46:13.770 --> 02:46:15.680 Participants did 324 hour dietary

NOTE Confidence: 0.88337490625

02:46:15.680 --> 02:46:18.198 recalls and provided a stool sample

NOTE Confidence: 0.88337490625

02:46:18.198 --> 02:46:20.386 for shotgun metagenomic sequencing

NOTE Confidence: 0.88337490625

02:46:20.386 --> 02:46:22.574 and untargeted metabolomics profiling.

NOTE Confidence: 0.736762132666667

02:46:25.720 --> 02:46:28.976 Just a brief word on the hold that

NOTE Confidence: 0.736762132666667

02:46:28.976 --> 02:46:31.631 hold genome shotgun sequencing as

NOTE Confidence: 0.736762132666667

02:46:31.631 --> 02:46:34.024 compared to 16 Sr RNA sequencing,

NOTE Confidence: 0.736762132666667

02:46:34.024 --> 02:46:36.614 which was used in the majority of the

NOTE Confidence: 0.736762132666667

02:46:36.614 --> 02:46:38.339 microbiome work and kidney stones,

NOTE Confidence: 0.736762132666667

02:46:38.340 --> 02:46:40.254 which sequence is only a single

NOTE Confidence: 0.736762132666667

02:46:40.254 --> 02:46:41.940 region of the bacterial genome

NOTE Confidence: 0.736762132666667

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02:46:41.940 --> 02:46:45.468 called genome shotgun sequencing.

NOTE Confidence: 0.736762132666667

02:46:45.470 --> 02:46:47.210 Sequences several random fragments of

NOTE Confidence: 0.736762132666667

02:46:47.210 --> 02:46:49.350 the genome and the major advantages

NOTE Confidence: 0.736762132666667

02:46:49.350 --> 02:46:51.744 that tax that can be more accurately

NOTE Confidence: 0.736762132666667

02:46:51.744 --> 02:46:53.500 identified at the species level.

NOTE Confidence: 0.845313565714286

02:46:57.090 --> 02:46:59.568 So this is data from that study.

NOTE Confidence: 0.845313565714286

02:46:59.570 --> 02:47:01.600 This shows a heat map of bacterial

NOTE Confidence: 0.845313565714286

02:47:01.600 --> 02:47:03.663 taxa and children with kidney stones

NOTE Confidence: 0.845313565714286

02:47:03.663 --> 02:47:05.548 and their matched healthy controls.

NOTE Confidence: 0.845313565714286

02:47:05.550 --> 02:47:07.908 Each column represents 1 fecal sample,

NOTE Confidence: 0.845313565714286

02:47:07.910 --> 02:47:11.767 and each row represents 1 bacterial taxon.

NOTE Confidence: 0.845313565714286

02:47:11.770 --> 02:47:14.108 The tax were included if the abundance

NOTE Confidence: 0.845313565714286

02:47:14.108 --> 02:47:16.339 in any sample exceeded point 1%,

NOTE Confidence: 0.845313565714286

02:47:16.340 --> 02:47:18.212 with the exception of axle bacteria

NOTE Confidence: 0.845313565714286

02:47:18.212 --> 02:47:19.970 and axial vector for migenes,

NOTE Confidence: 0.845313565714286

02:47:19.970 --> 02:47:21.875 which were included despite their

NOTE Confidence: 0.845313565714286

02:47:21.875 --> 02:47:23.780 lower abundance due to their

NOTE Confidence: 0.845313565714286

02:47:23.851 --> 02:47:26.126 presumed role in oxalate degradation.

NOTE Confidence: 0.845313565714286

02:47:26.130 --> 02:47:28.260 The overall taxonomic profile of the

NOTE Confidence: 0.845313565714286

02:47:28.260 --> 02:47:30.040 gut microbiome among participants with

NOTE Confidence: 0.845313565714286

02:47:30.040 --> 02:47:31.864 kidney stones and controls was similar

NOTE Confidence: 0.845313565714286

02:47:31.864 --> 02:47:33.848 to that observed in previous studies,

NOTE Confidence: 0.845313565714286

02:47:33.850 --> 02:47:35.835 where the Bacteroidetes and Clostridia

NOTE Confidence: 0.845313565714286

02:47:35.835 --> 02:47:37.820 species accounted for most of

NOTE Confidence: 0.845313565714286

02:47:37.887 --> 02:47:39.582 the bacterial population and you

NOTE Confidence: 0.845313565714286

02:47:39.582 --> 02:47:41.623 can see the very abundant species

NOTE Confidence: 0.845313565714286

02:47:41.623 --> 02:47:43.618 are the ones in orange and red.

NOTE Confidence: 0.860787762222222

02:47:49.400 --> 02:47:51.175 So to compare the taxonomic

NOTE Confidence: 0.860787762222222

02:47:51.175 --> 02:47:52.595 composition of all participants,

NOTE Confidence: 0.860787762222222

02:47:52.600 --> 02:47:54.574 we tested 91 bacterial techs of

NOTE Confidence: 0.860787762222222

02:47:54.574 --> 02:47:56.760 that had that greater than point 1%

NOTE Confidence: 0.860787762222222

02:47:56.760 --> 02:47:59.987 abundance and at least one stool sample.

NOTE Confidence: 0.860787762222222

02:47:59.990 --> 02:48:01.970 And we found that 31 bacterial

NOTE Confidence: 0.860787762222222

02:48:01.970 --> 02:48:03.773 techs are different in abundance

NOTE Confidence: 0.860787762222222

02:48:03.773 --> 02:48:05.441 between participants with kidney

NOTE Confidence: 0.860787762222222

02:48:05.441 --> 02:48:07.983 stones and controls at a predefined

NOTE Confidence: 0.860787762222222

02:48:07.983 --> 02:48:10.317 FDR adjusted threshold of less than

NOTE Confidence: 0.860787762222222

02:48:10.317 --> 02:48:12.410 .05 of the tax that identified,

NOTE Confidence: 0.860787762222222

02:48:12.410 --> 02:48:15.200 all were less abundant among participants

NOTE Confidence: 0.860787762222222

02:48:15.200 --> 02:48:18.119 who formed kidney stones than controls.

NOTE Confidence: 0.860787762222222

02:48:18.120 --> 02:48:19.315 And these included seven tasks

NOTE Confidence: 0.860787762222222

02:48:19.315 --> 02:48:20.800 that the produced the short chain.

NOTE Confidence: 0.860787762222222

02:48:20.800 --> 02:48:22.160 Fatty acid butyrate including

NOTE Confidence: 0.860787762222222

02:48:22.160 --> 02:48:23.180 several rose buria,

NOTE Confidence: 0.860787762222222

02:48:23.180 --> 02:48:25.050 and Clostridium species and those

NOTE Confidence: 0.860787762222222

02:48:25.050 --> 02:48:28.740 are highlighted with the red squares

NOTE Confidence: 0.860787762222222

02:48:28.740 --> 02:48:31.148 as well as lower abundance of three

NOTE Confidence: 0.860787762222222

02:48:31.148 --> 02:48:32.672 oxalate degrading bacterial taxa

NOTE Confidence: 0.860787762222222

02:48:32.672 --> 02:48:34.420 attacks that Enterococcus vocalist,

NOTE Confidence: 0.860787762222222

02:48:34.420 --> 02:48:37.252 Enterococcus PCM and Bifidobacterium

NOTE Confidence: 0.860787762222222

02:48:37.252 --> 02:48:40.792 Animalis the the lavender boxes.

NOTE Confidence: 0.860787762222222

02:48:40.800 --> 02:48:41.116 Correspondingly,

NOTE Confidence: 0.860787762222222

02:48:41.116 --> 02:48:43.012 the figure on the right shows

NOTE Confidence: 0.860787762222222

02:48:43.012 --> 02:48:44.550 that the gene abundance,

NOTE Confidence: 0.860787762222222

02:48:44.550 --> 02:48:45.597 beautiful Cohen dehydrogenase,

NOTE Confidence: 0.860787762222222

02:48:45.597 --> 02:48:47.691 the key bacterial enzyme in the

NOTE Confidence: 0.860787762222222

02:48:47.691 --> 02:48:49.029 butyrate production pathway,

NOTE Confidence: 0.860787762222222

02:48:49.030 --> 02:48:50.860 was also lower among the

NOTE Confidence: 0.860787762222222

02:48:50.860 --> 02:48:52.324 stone formers than controls.

NOTE Confidence: 0.61577540625

02:48:56.320 --> 02:48:59.812 So looking at the fecal sorry

NOTE Confidence: 0.61577540625

02:48:59.812 --> 02:49:01.339 fecal metabolome, overall,

NOTE Confidence: 0.61577540625

02:49:01.339 --> 02:49:03.134 the profile of fecal metabolites

NOTE Confidence: 0.61577540625

02:49:03.134 --> 02:49:04.570 was similar between participants

NOTE Confidence: 0.61577540625

02:49:04.625 --> 02:49:06.180 with kidney stones and controls.

NOTE Confidence: 0.61577540625

02:49:06.180 --> 02:49:08.259 But we carried out a linear discriminant

NOTE Confidence: 0.61577540625

02:49:08.259 --> 02:49:09.882 analysis to determine if a subset

NOTE Confidence: 0.61577540625

02:49:09.882 --> 02:49:11.232 of the metabolites could be used

NOTE Confidence: 0.61577540625

02:49:11.232 --> 02:49:13.023 to distinguish the two groups and

NOTE Confidence: 0.61577540625

02:49:13.023 --> 02:49:14.533 found that a linear discriminant

NOTE Confidence: 0.61577540625

02:49:14.540 --> 02:49:16.340 separated those with kidney stones

NOTE Confidence: 0.61577540625

02:49:16.340 --> 02:49:18.204 from controls with 77% accuracy.

NOTE Confidence: 0.61577540625

02:49:18.204 --> 02:49:20.556 There were 18 metabolites that were

NOTE Confidence: 0.61577540625

02:49:20.556 --> 02:49:21.727 significantly different between

NOTE Confidence: 0.61577540625

02:49:21.727 --> 02:49:23.039 participants with kidney stones

NOTE Confidence: 0.61577540625

02:49:23.039 --> 02:49:25.270 and controls at a pre specified.

NOTE Confidence: 0.61577540625

02:49:25.270 --> 02:49:27.478 Nominal P value of less than .01 ten,

NOTE Confidence: 0.61577540625

02:49:27.480 --> 02:49:30.120 being higher among cases.

NOTE Confidence: 0.61577540625

02:49:30.120 --> 02:49:31.996 Sorry to think it 10 being higher,

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NOTE Confidence: 0.61577540625

02:49:32.000 --> 02:49:34.232 my cases and eight metabolites being

NOTE Confidence: 0.61577540625

02:49:34.232 --> 02:49:36.380 lower one cases than controls.

NOTE Confidence: 0.61577540625

02:49:36.380 --> 02:49:37.434 And importantly,

NOTE Confidence: 0.61577540625

02:49:37.434 --> 02:49:40.069 these differences in fecal metabolites

NOTE Confidence: 0.61577540625

02:49:40.069 --> 02:49:42.370 associated with bacterial abundance.

NOTE Confidence: 0.61577540625

02:49:42.370 --> 02:49:43.858 So you can see in the right hand

NOTE Confidence: 0.61577540625

02:49:43.858 --> 02:49:45.857 side of the figure that we computed

NOTE Confidence: 0.61577540625

02:49:45.857 --> 02:49:47.121 a correlation matrix between

NOTE Confidence: 0.61577540625

02:49:47.121 --> 02:49:48.510 metabolites and species abundance,

NOTE Confidence: 0.61577540625

02:49:48.510 --> 02:49:50.105 which revealed strong correlations for

NOTE Confidence: 0.61577540625

02:49:50.105 --> 02:49:52.679 many of the texts on metabolite pairs.

NOTE Confidence: 0.81725593

02:49:57.540 --> 02:49:59.780 So, following this untargeted analysis,

NOTE Confidence: 0.81725593

02:49:59.780 --> 02:50:03.218 we focused on oxalate degrading bacteria,

NOTE Confidence: 0.81725593

02:50:03.220 --> 02:50:05.460 and we constructed an abundance

NOTE Confidence: 0.81725593

02:50:05.460 --> 02:50:08.200 correlation network on the left panel,

NOTE Confidence: 0.81725593

02:50:08.200 --> 02:50:10.088 a proxy degrading bacteria

NOTE Confidence: 0.81725593

02:50:10.088 --> 02:50:11.976 detected in this study,

NOTE Confidence: 0.81725593

02:50:11.980 --> 02:50:14.458 and we found that it consisted of

NOTE Confidence: 0.81725593

02:50:14.458 --> 02:50:16.290 positive correlations among the isolated

NOTE Confidence: 0.81725593

02:50:16.290 --> 02:50:18.414 degrade oxalate degrading tax set and

NOTE Confidence: 0.81725593

02:50:18.414 --> 02:50:20.868 lacked any strong negative correlations.

NOTE Confidence: 0.81725593

02:50:20.870 --> 02:50:22.865 The network really consisted of two modules,

NOTE Confidence: 0.81725593

02:50:22.870 --> 02:50:25.370 1 populated by relatively high

NOTE Confidence: 0.81725593

02:50:25.370 --> 02:50:27.370 abundance oxalate degrading taxa.

NOTE Confidence: 0.81725593

02:50:27.370 --> 02:50:29.018 And this is panel B and the other

NOTE Confidence: 0.81725593

02:50:29.018 --> 02:50:30.680 by low abundance lactobacilli.

NOTE Confidence: 0.831588171538462

02:50:34.950 --> 02:50:37.386 So importantly, what's shown here is the

NOTE Confidence: 0.831588171538462

02:50:37.386 --> 02:50:39.608 alpha diversity of the gut microbiome.

NOTE Confidence: 0.831588171538462

02:50:39.610 --> 02:50:41.394 So in the left hand figure you can

NOTE Confidence: 0.831588171538462

02:50:41.394 --> 02:50:43.449 see that we corroborated findings in

NOTE Confidence: 0.831588171538462

02:50:43.449 --> 02:50:45.394 adults showing lower diversity and

NOTE Confidence: 0.831588171538462

02:50:45.394 --> 02:50:47.081 participants with kidney stones compared

NOTE Confidence: 0.831588171538462

02:50:47.081 --> 02:50:48.947 to controls assessed both by the

NOTE Confidence: 0.831588171538462

02:50:48.950 --> 02:50:52.850 richness and Shannon's diversity index.

NOTE Confidence: 0.831588171538462

02:50:52.850 --> 02:50:54.760 And strikingly, the alpha diversity

NOTE Confidence: 0.831588171538462

02:50:54.760 --> 02:50:56.670 exhibited an age dependent association

NOTE Confidence: 0.831588171538462

02:50:56.724 --> 02:50:58.169 in those with kidney stones,

NOTE Confidence: 0.831588171538462

02:50:58.170 --> 02:50:59.018 but not in control.

NOTE Confidence: 0.831588171538462

02:50:59.018 --> 02:51:01.391 So as you can see in the right hand

NOTE Confidence: 0.831588171538462

02:51:01.391 --> 02:51:03.136 figure bacterial diversity first decreased

NOTE Confidence: 0.831588171538462

02:51:03.136 --> 02:51:05.188 and then increased with age among

NOTE Confidence: 0.831588171538462

02:51:05.188 --> 02:51:07.126 those who were kidney stone formers,

NOTE Confidence: 0.831588171538462

02:51:07.130 --> 02:51:09.308 with the lowest diversity found among

NOTE Confidence: 0.831588171538462

02:51:09.308 --> 02:51:11.108 individuals who first formed kidney

NOTE Confidence: 0.831588171538462

02:51:11.108 --> 02:51:13.404 stones between 9:00 and 14 years of age.

NOTE Confidence: 0.831588171538462

02:51:13.410 --> 02:51:14.052 In contrast,

NOTE Confidence: 0.831588171538462

02:51:14.052 --> 02:51:15.978 the alpha diversity of the microbiome

NOTE Confidence: 0.831588171538462

02:51:15.978 --> 02:51:17.539 of participants who are controls

NOTE Confidence: 0.831588171538462

02:51:17.539 --> 02:51:18.974 with similar across the spectrum

NOTE Confidence: 0.831588171538462

02:51:18.974 --> 02:51:20.555 and there were no significant

NOTE Confidence: 0.831588171538462

02:51:20.555 --> 02:51:22.140 associations found with the age.

NOTE Confidence: 0.871142304545454

02:51:25.760 --> 02:51:27.085 So to summarize, this study

NOTE Confidence: 0.871142304545454

02:51:27.085 --> 02:51:28.940 showed the loss of gut bacteria,

NOTE Confidence: 0.871142304545454

02:51:28.940 --> 02:51:30.468 particularly those that produce

NOTE Confidence: 0.871142304545454

02:51:30.468 --> 02:51:31.996 butyrate and degrade oxalate,

NOTE Confidence: 0.871142304545454

02:51:32.000 --> 02:51:33.544 were associated with perturbations

NOTE Confidence: 0.871142304545454

02:51:33.544 --> 02:51:35.430 of the metabolome that may

NOTE Confidence: 0.871142304545454

02:51:35.430 --> 02:51:36.910 be upstream determinants of

NOTE Confidence: 0.871142304545454

02:51:36.910 --> 02:51:38.520 early onset calcium oxalate,

NOTE Confidence: 0.871142304545454

02:51:38.520 --> 02:51:39.579 kidney stone disease.

NOTE Confidence: 0.848577370526316

02:51:42.350 --> 02:51:45.158 So I just want to shift to highlight

NOTE Confidence: 0.848577370526316

02:51:45.158 --> 02:51:47.060 some current work we're doing

NOTE Confidence: 0.848577370526316

02:51:47.060 --> 02:51:49.304 to follow up on these signals.

NOTE Confidence: 0.848577370526316

02:51:49.310 --> 02:51:51.370 So our active investigations are

NOTE Confidence: 0.848577370526316

02:51:51.370 --> 02:51:53.430 really seeking to further characterize

NOTE Confidence: 0.848577370526316

02:51:53.492 --> 02:51:55.544 the microbiome and determine how the

NOTE Confidence: 0.848577370526316

02:51:55.544 --> 02:51:57.498 composition of the gut microbiome

NOTE Confidence: 0.848577370526316

02:51:57.498 --> 02:51:59.586 affects urinary mineral excretion.

NOTE Confidence: 0.848577370526316

02:51:59.590 --> 02:52:01.662 The goal is that ultimately we can

NOTE Confidence: 0.848577370526316

02:52:01.662 --> 02:52:03.663 identify how we can restore the

NOTE Confidence: 0.848577370526316

02:52:03.663 --> 02:52:05.403 gut microbiome or its function,

NOTE Confidence: 0.848577370526316

02:52:05.410 --> 02:52:07.270 and our hypothesis is that understanding

NOTE Confidence: 0.848577370526316

02:52:07.270 --> 02:52:09.180 the gut kidney access will introduce

NOTE Confidence: 0.848577370526316

02:52:09.180 --> 02:52:11.040 a new paradigm for primary and

NOTE Confidence: 0.848577370526316

02:52:11.040 --> 02:52:12.560 secondary kidney stone prevention.

NOTE Confidence: 0.86301888125

02:52:15.950 --> 02:52:19.166 So the active study that we were conducting,

NOTE Confidence: 0.86301888125

02:52:19.170 --> 02:52:20.774 called the pursuing optimal

NOTE Confidence: 0.86301888125

02:52:20.774 --> 02:52:22.779 organisms and people with stones.

NOTE Confidence: 0.86301888125

02:52:22.780 --> 02:52:24.928 Consists of a patient oriented study

NOTE Confidence: 0.86301888125

02:52:24.928 --> 02:52:27.756 as well as a A data analysis study

NOTE Confidence: 0.86301888125

02:52:27.756 --> 02:52:30.320 that I'll show you in a moment.

NOTE Confidence: 0.86301888125

02:52:30.320 --> 02:52:32.576 This is really an expansion of

NOTE Confidence: 0.86301888125

02:52:32.576 --> 02:52:34.560 our earlier case control study.

NOTE Confidence: 0.86301888125

02:52:34.560 --> 02:52:37.626 We're enrolling 300 children and adults,

NOTE Confidence: 0.86301888125

02:52:37.630 --> 02:52:41.260 150 cases and 150 controls,

NOTE Confidence: 0.86301888125

02:52:41.260 --> 02:52:43.595 and this study is using

NOTE Confidence: 0.86301888125

02:52:43.595 --> 02:52:44.996 comprehensive nutritional profiling,

NOTE Confidence: 0.86301888125

02:52:45.000 --> 02:52:46.371 high throughput microbiome,

NOTE Confidence: 0.86301888125

02:52:46.371 --> 02:52:48.199 and metabolomic data analysis,

NOTE Confidence: 0.86301888125

02:52:48.200 --> 02:52:49.928 as well as large database analytics

NOTE Confidence: 0.86301888125

02:52:49.928 --> 02:52:52.489 really to try and define how diet and

NOTE Confidence: 0.86301888125

02:52:52.489 --> 02:52:54.174 antibiotics perturb the gut microbiome

NOTE Confidence: 0.86301888125

02:52:54.174 --> 02:52:56.503 and how the resulting changes in

NOTE Confidence: 0.86301888125

02:52:56.503 --> 02:52:58.047 downstream metabolites and chemistries

NOTE Confidence: 0.86301888125

02:52:58.047 --> 02:52:59.940 and intestinal and urinary tracts

NOTE Confidence: 0.86301888125

02:52:59.940 --> 02:53:01.815 contribute to kidney stone disease.

NOTE Confidence: 0.86301888125

02:53:01.820 --> 02:53:03.656 So, in this patient oriented study,

NOTE Confidence: 0.86301888125

02:53:03.660 --> 02:53:04.386 individuals.

NOTE Confidence: 0.86301888125

02:53:04.386 --> 02:53:06.564 Undergoing nutritional profiling

NOTE Confidence: 0.86301888125

02:53:06.564 --> 02:53:08.886 with 24 hour diet recalls

NOTE Confidence: 0.86301888125

02:53:08.886 --> 02:53:10.083 shotgun metagenomic sequencing

NOTE Confidence: 0.86301888125

02:53:10.083 --> 02:53:12.124 of stool targeted and untargeted

NOTE Confidence: 0.86301888125

02:53:12.124 --> 02:53:14.069 metabolomics of stool and urine.

NOTE Confidence: 0.86301888125

02:53:14.070 --> 02:53:15.825 24 hour urine chemistries and

NOTE Confidence: 0.86301888125

02:53:15.825 --> 02:53:17.580 then we will perform compositional

NOTE Confidence: 0.86301888125

02:53:17.635 --> 02:53:18.971 mediation analysis to discover

NOTE Confidence: 0.86301888125

02:53:18.971 --> 02:53:20.975 how the gut microbiome and its

NOTE Confidence: 0.86301888125

02:53:21.036 --> 02:53:22.203 downstream metabolites mediates

NOTE Confidence: 0.86301888125

02:53:22.203 --> 02:53:24.148 the direct and indirect effects

NOTE Confidence: 0.86301888125

02:53:24.148 --> 02:53:25.989 of diet on kidney stones.

NOTE Confidence: 0.887367943333333

02:53:28.110 --> 02:53:30.995 Complementary to this approach,

NOTE Confidence: 0.887367943333333

02:53:30.995 --> 02:53:32.720 we are partnering with health

NOTE Confidence: 0.887367943333333

02:53:32.720 --> 02:53:34.706 core and leveraging the healthcare

NOTE Confidence: 0.887367943333333

02:53:34.706 --> 02:53:36.350 integrated research database,

NOTE Confidence: 0.887367943333333

02:53:36.350 --> 02:53:38.250 which is a longitudinally integrated

NOTE Confidence: 0.887367943333333

02:53:38.250 --> 02:53:40.150 medical and pharmacy claims database.

NOTE Confidence: 0.887367943333333

02:53:40.150 --> 02:53:42.748 Drawn from healthcare encounters of members

NOTE Confidence: 0.887367943333333

02:53:42.748 --> 02:53:45.299 enrolled in several commercial health plans.

NOTE Confidence: 0.887367943333333

02:53:45.300 --> 02:53:47.796 This is a extension of our work in

NOTE Confidence: 0.887367943333333

02:53:47.796 --> 02:53:50.020 the United Kingdom thin database.

NOTE Confidence: 0.887367943333333

02:53:50.020 --> 02:53:52.428 You can see we have a much larger

NOTE Confidence: 0.887367943333333

02:53:52.428 --> 02:53:54.276 sample size of over 600,000 individuals

NOTE Confidence: 0.887367943333333

02:53:54.276 --> 02:53:57.100 who were four to 65 years of age

NOTE Confidence: 0.887367943333333

02:53:57.175 --> 02:53:59.415 at the time of their first stone.

NOTE Confidence: 0.887367943333333

02:53:59.420 --> 02:54:02.900 We've cut off at 65 because of the

NOTE Confidence: 0.887367943333333

02:54:02.900 --> 02:54:04.960 introduction of Medicare at 65.

NOTE Confidence: 0.887367943333333

02:54:04.960 --> 02:54:07.800 So the.

NOTE Confidence: 0.887367943333333

02:54:07.800 --> 02:54:09.708 With the data in this database,

NOTE Confidence: 0.887367943333333

02:54:09.710 --> 02:54:13.215 then becomes less complete and

NOTE Confidence: 0.887367943333333

02:54:13.215 --> 02:54:17.240 then we have matched 5 to one

NOTE Confidence: 0.887367943333333

02:54:17.240 --> 02:54:19.432 for controls using incidence,

NOTE Confidence: 0.887367943333333

02:54:19.432 --> 02:54:21.560 density, sampling, match and age,

NOTE Confidence: 0.887367943333333

02:54:21.560 --> 02:54:23.140 sex and geographic region.

NOTE Confidence: 0.887367943333333

02:54:23.140 --> 02:54:26.200 So over 3,000,000 controls.

NOTE Confidence: 0.887367943333333

02:54:26.200 --> 02:54:28.072 So we'll be doing a nested

NOTE Confidence: 0.887367943333333

02:54:28.072 --> 02:54:29.008 case control study,

NOTE Confidence: 0.887367943333333

02:54:29.010 --> 02:54:30.378 determine the dose response

NOTE Confidence: 0.887367943333333

02:54:30.378 --> 02:54:31.404 relationship between antibiotic

NOTE Confidence: 0.887367943333333

02:54:31.404 --> 02:54:32.780 exposure and kidney stones,

NOTE Confidence: 0.887367943333333

02:54:32.780 --> 02:54:34.684 and to really try and identify subgroups

NOTE Confidence: 0.887367943333333

02:54:34.684 --> 02:54:36.615 at greatest risk for development of

NOTE Confidence: 0.887367943333333

02:54:36.615 --> 02:54:38.380 kidney stones after antibiotic exposure,

NOTE Confidence: 0.887367943333333

02:54:38.380 --> 02:54:41.320 and delve more into the age specific

NOTE Confidence: 0.887367943333333

02:54:41.320 --> 02:54:44.720 patterns in kidney stone risk.

NOTE Confidence: 0.887367943333333

02:54:44.720 --> 02:54:47.506 We will then also use a subset

NOTE Confidence: 0.887367943333333

02:54:47.506 --> 02:54:49.315 of of this population,

NOTE Confidence: 0.887367943333333

02:54:49.315 --> 02:54:53.620 so focusing on the kidney stone population,

NOTE Confidence: 0.887367943333333

02:54:53.620 --> 02:54:55.850 linking with LabCorp to link

NOTE Confidence: 0.887367943333333

02:54:55.850 --> 02:54:58.080 to their Litho link analysis.

NOTE Confidence: 0.887367943333333

02:54:58.080 --> 02:54:59.412 So we estimate this is going

NOTE Confidence: 0.887367943333333

02:54:59.412 --> 02:55:01.092 to be over 200,000 individuals.

NOTE Confidence: 0.887367943333333

02:55:01.092 --> 02:55:03.622 We've linked using privacy preserving

NOTE Confidence: 0.887367943333333

02:55:03.622 --> 02:55:05.859 record linkage with their lethal

NOTE Confidence: 0.887367943333333

02:55:05.859 --> 02:55:08.451 link data and the goal of this second

NOTE Confidence: 0.887367943333333

02:55:08.523 --> 02:55:11.169 analysis is to identify how oral

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NOTE Confidence: 0.887367943333333

02:55:11.169 --> 02:55:12.933 antibiotics alter urine chemistries

NOTE Confidence: 0.887367943333333

02:55:12.940 --> 02:55:14.790 among individuals with kidney stones.

NOTE Confidence: 0.862448218181818

02:55:17.670 --> 02:55:19.315 Just want to highlight several

NOTE Confidence: 0.862448218181818

02:55:19.315 --> 02:55:21.310 areas of innovation in this work,

NOTE Confidence: 0.862448218181818

02:55:21.310 --> 02:55:24.026 which is again the use of shotgun

NOTE Confidence: 0.862448218181818

02:55:24.026 --> 02:55:26.037 metagenomic sequencing of the gut

NOTE Confidence: 0.862448218181818

02:55:26.037 --> 02:55:28.365 microbiome and contrast to most prior

NOTE Confidence: 0.862448218181818

02:55:28.365 --> 02:55:30.529 studies using 16 S RNA sequencing.

NOTE Confidence: 0.862448218181818

02:55:30.530 --> 02:55:32.498 Leveraging untargeted, untargeted,

NOTE Confidence: 0.862448218181818

02:55:32.498 --> 02:55:36.434 metabolomic profiling of stool and urine.

NOTE Confidence: 0.862448218181818

02:55:36.440 --> 02:55:38.080 Examining kidney stone disease.

NOTE Confidence: 0.862448218181818

02:55:38.080 --> 02:55:39.720 Really across the lifespan,

NOTE Confidence: 0.862448218181818

02:55:39.720 --> 02:55:41.604 so including children and adults so

NOTE Confidence: 0.862448218181818

02:55:41.604 --> 02:55:43.610 that we can understand each specific

NOTE Confidence: 0.862448218181818

02:55:43.610 --> 02:55:45.686 perturbations of the gut kidney access

NOTE Confidence: 0.862448218181818

02:55:45.686 --> 02:55:47.579 and calcium kidney stone disease.

NOTE Confidence: 0.862448218181818

02:55:47.580 --> 02:55:50.485 And this novel linkage of 24 year

NOTE Confidence: 0.862448218181818

02:55:50.485 --> 02:55:52.293 old chemistries with pharmaceutical

NOTE Confidence: 0.862448218181818

02:55:52.293 --> 02:55:55.660 claims data which will allow us to.

NOTE Confidence: 0.862448218181818

02:55:55.660 --> 02:55:57.672 Really evaluate how antibiotic

NOTE Confidence: 0.862448218181818

02:55:57.672 --> 02:55:59.718 exposure impacts your own chemistries.

NOTE Confidence: 0.8550244605

02:56:04.250 --> 02:56:06.797 So now I want to shift from origins to

NOTE Confidence: 0.8550244605

02:56:06.797 --> 02:56:08.742 complications and talk about a different

NOTE Confidence: 0.8550244605

02:56:08.742 --> 02:56:10.347 access and kidney stone disease,

NOTE Confidence: 0.8550244605

02:56:10.350 --> 02:56:14.388 and that's the bone vascular access.

NOTE Confidence: 0.8550244605

02:56:14.390 --> 02:56:16.320 More than the episodic occurrence

NOTE Confidence: 0.8550244605

02:56:16.320 --> 02:56:17.864 of debilitating stone events,

NOTE Confidence: 0.8550244605

02:56:17.870 --> 02:56:19.715 kidney stone disease is increasingly

NOTE Confidence: 0.8550244605

02:56:19.715 --> 02:56:21.560 recognized as a chronic systemic

NOTE Confidence: 0.8550244605

02:56:21.614 --> 02:56:23.864 disorder of mineral homeostasis with

NOTE Confidence: 0.8550244605

02:56:23.864 --> 02:56:25.466 considerable morbidity including increased

NOTE Confidence: 0.8550244605

02:56:25.466 --> 02:56:27.206 risk for chronic kidney disease,

NOTE Confidence: 0.8550244605

02:56:27.210 --> 02:56:29.360 bone fracture, and cardiovascular disease.

NOTE Confidence: 0.851555221666667

02:56:32.680 --> 02:56:37.160 So we and others have shown increased risk

NOTE Confidence: 0.851555221666667

02:56:37.160 --> 02:56:40.100 of impaired bone health in individuals.

NOTE Confidence: 0.851555221666667

02:56:40.100 --> 02:56:43.404 Kidney stone with an increased risk of

NOTE Confidence: 0.851555221666667

02:56:43.404 --> 02:56:45.600 fracture, increased risk of hypertension,

NOTE Confidence: 0.851555221666667

02:56:45.600 --> 02:56:48.180 increased risk of coronary disease as

NOTE Confidence: 0.851555221666667

02:56:48.251 --> 02:56:50.495 well as kidney function decline and

NOTE Confidence: 0.851555221666667

02:56:50.495 --> 02:56:52.771 progression to end stage kidney disease

NOTE Confidence: 0.851555221666667

02:56:52.771 --> 02:56:55.611 and what's striking from this body of work

NOTE Confidence: 0.851555221666667

02:56:55.620 --> 02:56:59.484 is the signal of a increased magnitude.

NOTE Confidence: 0.851555221666667

02:56:59.490 --> 02:57:01.545 Of risk observed in younger

NOTE Confidence: 0.851555221666667

02:57:01.545 --> 02:57:03.189 individuals and among women.

NOTE Confidence: 0.851555221666667

02:57:03.190 --> 02:57:05.598 So what does that mean for the risk

NOTE Confidence: 0.851555221666667

02:57:05.598 --> 02:57:07.404 of individuals who start forming

NOTE Confidence: 0.851555221666667

02:57:07.404 --> 02:57:08.547 stones in childhood?

NOTE Confidence: 0.851555221666667

02:57:08.550 --> 02:57:10.428 Because this is largely adult data.

NOTE Confidence: 0.651837518888889

02:57:13.700 --> 02:57:15.830 This picture highlights full and

NOTE Confidence: 0.651837518888889

02:57:15.830 --> 02:57:17.534 mineral accrual and childhood.

NOTE Confidence: 0.651837518888889

02:57:17.540 --> 02:57:19.364 It's important to recognize that peak

NOTE Confidence: 0.651837518888889

02:57:19.364 --> 02:57:21.502 bone mass is a lifelong determinant

NOTE Confidence: 0.651837518888889

02:57:21.502 --> 02:57:24.174 of osteoporosis and 90% of that peak

NOTE Confidence: 0.651837518888889

02:57:24.174 --> 02:57:26.400 bone mass is established by age 18.

NOTE Confidence: 0.651837518888889

02:57:26.400 --> 02:57:28.695 Although we do continue to

NOTE Confidence: 0.651837518888889

02:57:28.695 --> 02:57:31.320 cortical density up until age 30.

NOTE Confidence: 0.651837518888889

02:57:31.320 --> 02:57:33.581 And about 1/4 of the adult skeletal

NOTE Confidence: 0.651837518888889

02:57:33.581 --> 02:57:35.479 mass is actually laid down in

NOTE Confidence: 0.651837518888889

02:57:35.479 --> 02:57:37.195 the two year period of around

NOTE Confidence: 0.651837518888889

02:57:37.195 --> 02:57:39.228 the time of peak linear growth.

NOTE Confidence: 0.651837518888889

02:57:39.230 --> 02:57:40.622 In the growing skeleton,

NOTE Confidence: 0.651837518888889

02:57:40.622 --> 02:57:42.014 positive calcium balance is

NOTE Confidence: 0.651837518888889

02:57:42.014 --> 02:57:43.810 favored in order to achieve

NOTE Confidence: 0.651837518888889

02:57:43.810 --> 02:57:45.540 calcium retention and build bone.

NOTE Confidence: 0.834328233076923

02:57:49.660 --> 02:57:52.140 Again, what I want to highlight here is

NOTE Confidence: 0.834328233076923

02:57:52.140 --> 02:57:53.830 fracture epidemiology in healthy children,

NOTE Confidence: 0.834328233076923

02:57:53.830 --> 02:57:56.098 so fractures are not rare events in

NOTE Confidence: 0.834328233076923

02:57:56.098 --> 02:57:58.089 childhood and this is Seminole work

NOTE Confidence: 0.834328233076923

02:57:58.089 --> 02:58:00.315 done nearly two two decades ago now,

NOTE Confidence: 0.834328233076923

02:58:00.320 --> 02:58:02.846 but has been reproduced in several

NOTE Confidence: 0.834328233076923

02:58:02.846 --> 02:58:05.889 studies since showing distinct age and sex

NOTE Confidence: 0.834328233076923

02:58:05.889 --> 02:58:08.034 specific patterns and fracture incidents.

NOTE Confidence: 0.834328233076923

02:58:08.040 --> 02:58:10.461 With a peak age of about 14 in males

NOTE Confidence: 0.834328233076923

02:58:10.461 --> 02:58:12.581 and 11 years in females and this

NOTE Confidence: 0.834328233076923

02:58:12.581 --> 02:58:15.119 peak in 14 year old males are about

NOTE Confidence: 0.834328233076923

02:58:15.120 --> 02:58:17.260 280 fractures per 10,000 person.

NOTE Confidence: 0.834328233076923

02:58:17.260 --> 02:58:19.136 Years is only surpassed at age 85

NOTE Confidence: 0.834328233076923

02:58:19.136 --> 02:58:21.088 and women and never again in men.

NOTE Confidence: 0.811315408095238

02:58:24.160 --> 02:58:26.488 So wanna spend just the most of the

NOTE Confidence: 0.811315408095238

02:58:26.488 --> 02:58:29.136 rest of the time talking about impaired

NOTE Confidence: 0.811315408095238

02:58:29.136 --> 02:58:32.174 bone health in kidney stone disease and

NOTE Confidence: 0.811315408095238

02:58:32.174 --> 02:58:35.138 thinking about mineral and bone disorder?

NOTE Confidence: 0.811315408095238

02:58:35.140 --> 02:58:38.668 MD in the context of kidney stone disease.

NOTE Confidence: 0.811315408095238

02:58:38.670 --> 02:58:40.998 So again, as a chronic systemic disorder of

NOTE Confidence: 0.811315408095238

02:58:40.998 --> 02:58:42.660 mental homeostasis that's disproportionately

NOTE Confidence: 0.811315408095238

02:58:42.660 --> 02:58:44.208 increasing among adolescents,

NOTE Confidence: 0.811315408095238

02:58:44.210 --> 02:58:46.429 we really need to think about how

NOTE Confidence: 0.811315408095238

02:58:46.429 --> 02:58:48.583 this may impact long term bone

NOTE Confidence: 0.811315408095238

02:58:48.583 --> 02:58:50.099 health in this population.

NOTE Confidence: 0.811315408095238

02:58:50.100 --> 02:58:52.608 There have been many decks of

NOTE Confidence: 0.811315408095238

02:58:52.608 --> 02:58:54.700 studies showing produced aerial bomb,

NOTE Confidence: 0.811315408095238

02:58:54.700 --> 02:58:56.830 mineral density and children and adults,

NOTE Confidence: 0.811315408095238

02:58:56.830 --> 02:58:58.948 and actually now more than four

NOTE Confidence: 0.811315408095238

02:58:58.948 --> 02:59:00.360 population based cohort studies

NOTE Confidence: 0.811315408095238

02:59:00.416 --> 02:59:01.709 demonstrating increased fracture

NOTE Confidence: 0.811315408095238

02:59:01.709 --> 02:59:04.295 incidence with the hazard ratio ranging

NOTE Confidence: 0.811315408095238

02:59:04.295 --> 02:59:06.500 from 1.08 to 1.2 and older adults.

NOTE Confidence: 0.856997096190476

02:59:08.770 --> 02:59:11.182 What I want to show you here is data

NOTE Confidence: 0.856997096190476

02:59:11.182 --> 02:59:14.092 from work that we did again in the

NOTE Confidence: 0.856997096190476

02:59:14.092 --> 02:59:15.850 health Improvement Network database.

NOTE Confidence: 0.856997096190476

02:59:15.850 --> 02:59:18.658 Where we looked at over 50,000

NOTE Confidence: 0.856997096190476

02:59:18.658 --> 02:59:21.044 individuals with kidney stones and

NOTE Confidence: 0.856997096190476

02:59:21.044 --> 02:59:23.666 compared them in a retrospective cohort

NOTE Confidence: 0.856997096190476

02:59:23.666 --> 02:59:26.116 study to over 500,000 individuals

NOTE Confidence: 0.856997096190476

02:59:26.116 --> 02:59:29.524 who did not have kidney stones.

NOTE Confidence: 0.856997096190476

02:59:29.530 --> 02:59:32.379 And what's shown here is the age

NOTE Confidence: 0.856997096190476

02:59:32.379 --> 02:59:35.190 and sex specific fracture incidence

NOTE Confidence: 0.856997096190476

02:59:35.190 --> 02:59:37.440 by decile of age in participants

NOTE Confidence: 0.856997096190476

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02:59:37.440 --> 02:59:39.480 with and without kidney stones.

NOTE Confidence: 0.83141748875

02:59:42.330 --> 02:59:44.026 This figure highlights it a little bit more.

NOTE Confidence: 0.83141748875

02:59:44.030 --> 02:59:47.400 The magnitude of this association.

NOTE Confidence: 0.83141748875

02:59:47.400 --> 02:59:49.692 So in emails there was an

NOTE Confidence: 0.83141748875

02:59:49.692 --> 02:59:51.506 overall hazard ratio of 1.13,

NOTE Confidence: 0.83141748875

02:59:51.506 --> 02:59:53.508 but I want to call your attention

NOTE Confidence: 0.83141748875

02:59:53.510 --> 02:59:56.354 to the 10 to 19 year old age window

NOTE Confidence: 0.83141748875

02:59:56.354 --> 02:59:59.192 in males where the hazard ratio

NOTE Confidence: 0.83141748875

02:59:59.192 --> 03:00:02.378 was actually 1.51 and females,

NOTE Confidence: 0.83141748875

03:00:02.378 --> 03:00:03.834 there was a statistically

NOTE Confidence: 0.83141748875

03:00:03.834 --> 03:00:05.290 significant interaction with age,

NOTE Confidence: 0.83141748875

03:00:05.290 --> 03:00:07.034 so we can't report an overall hazard ratio.

NOTE Confidence: 0.83141748875

03:00:07.040 --> 03:00:08.762 But you can see that the magnitude

NOTE Confidence: 0.83141748875

03:00:08.762 --> 03:00:10.326 of the hazard ratio was greatest

NOTE Confidence: 0.83141748875

03:00:10.326 --> 03:00:11.862 in the 4th decade of Life,

NOTE Confidence: 0.83141748875

03:00:11.870 --> 03:00:15.011 so 30 to 39 year old women and then

NOTE Confidence: 0.83141748875

03:00:15.011 --> 03:00:17.899 decreased to a hazard ratio of 1.21 and 8.

NOTE Confidence: 0.83141748875

03:00:17.899 --> 03:00:18.808 Decade of life.

NOTE Confidence: 0.83141748875

03:00:18.810 --> 03:00:20.790 It's important to note, however,

NOTE Confidence: 0.83141748875

03:00:20.790 --> 03:00:23.198 that with the with the rate of

NOTE Confidence: 0.83141748875

03:00:23.198 --> 03:00:24.589 osteoporotic fractures in the

NOTE Confidence: 0.83141748875

03:00:24.589 --> 03:00:26.329 8th decade of life and women,

NOTE Confidence: 0.83141748875

03:00:26.330 --> 03:00:28.826 this hazard ratio of 1.21 represents

NOTE Confidence: 0.83141748875

03:00:28.826 --> 03:00:31.020 a significant public health burden.

NOTE Confidence: 0.733827145555556

03:00:33.840 --> 03:00:36.336 So what is behind the increased

NOTE Confidence: 0.733827145555556

03:00:36.336 --> 03:00:39.047 fracture risk and reduce both mineral

NOTE Confidence: 0.733827145555556

03:00:39.047 --> 03:00:41.945 density in patients with kidney stones?

NOTE Confidence: 0.733827145555556

03:00:41.950 --> 03:00:45.109 And I think part of the issue with the

NOTE Confidence: 0.733827145555556

03:00:45.109 --> 03:00:47.403 existing literature is that there was

NOTE Confidence: 0.733827145555556

03:00:47.403 --> 03:00:50.580 a focus primarily on hypercalciuria,

NOTE Confidence: 0.733827145555556

03:00:50.580 --> 03:00:54.751 so this summarizes the literature on bone

NOTE Confidence: 0.733827145555556

285

03:00:54.751 --> 03:00:57.493 density in children with kidney stones,

NOTE Confidence: 0.733827145555556

03:00:57.500 --> 03:00:59.888 and you can see that overwhelmingly

NOTE Confidence: 0.733827145555556

03:00:59.888 --> 03:01:01.890 these studies looked at children

NOTE Confidence: 0.733827145555556

03:01:01.890 --> 03:01:03.120 with idiopathic hypercalciuria.

NOTE Confidence: 0.733827145555556

03:01:03.120 --> 03:01:05.170 With or without kidney stones,

NOTE Confidence: 0.733827145555556

03:01:05.170 --> 03:01:07.440 rather than looking at kidney

NOTE Confidence: 0.733827145555556

03:01:07.440 --> 03:01:10.463 kidney stones from a more agnostic

NOTE Confidence: 0.733827145555556

03:01:10.463 --> 03:01:13.107 perspective of underlying risk.

NOTE Confidence: 0.733827145555556

03:01:13.110 --> 03:01:14.965 The studies were cross sectional

NOTE Confidence: 0.733827145555556

03:01:14.965 --> 03:01:17.238 and again largely limited to aerial

NOTE Confidence: 0.733827145555556

03:01:17.238 --> 03:01:19.356 bone mineral density of the lumbar

NOTE Confidence: 0.733827145555556

03:01:19.356 --> 03:01:22.182 spine and Dexter does not allow to

NOTE Confidence: 0.733827145555556

03:01:22.182 --> 03:01:23.886 distinguish compartment density and

NOTE Confidence: 0.733827145555556

03:01:23.886 --> 03:01:26.201 particularly the lumbar spine prevents

NOTE Confidence: 0.733827145555556

03:01:26.201 --> 03:01:28.149 insights into cortical structure.

NOTE Confidence: 0.733827145555556

03:01:28.150 --> 03:01:30.052 Most of these studies did not

NOTE Confidence: 0.733827145555556

03:01:30.052 --> 03:01:31.003 include healthy controls,

NOTE Confidence: 0.733827145555556

03:01:31.010 --> 03:01:33.906 but you can see that the range of

NOTE Confidence: 0.733827145555556

03:01:33.906 --> 03:01:35.950 osteopenia was 22 to 54% across

NOTE Confidence: 0.733827145555556

03:01:35.950 --> 03:01:38.530 these studies and there were more

NOTE Confidence: 0.733827145555556

03:01:38.530 --> 03:01:40.275 pronounced deficits in stone

NOTE Confidence: 0.733827145555556

03:01:40.275 --> 03:01:42.729 formers than in children who had

NOTE Confidence: 0.733827145555556

03:01:42.729 --> 03:01:44.630 isolated idiopathic hypercalciuria.

NOTE Confidence: 0.733827145555556

03:01:44.630 --> 03:01:46.994 This table summarizes a review of

NOTE Confidence: 0.733827145555556

03:01:46.994 --> 03:01:49.306 preclinical and clinical data that really

NOTE Confidence: 0.733827145555556

03:01:49.306 --> 03:01:51.470 just drives home the point that it's

NOTE Confidence: 0.733827145555556

03:01:51.470 --> 03:01:53.600 probably not all about hypercalciuria,

NOTE Confidence: 0.733827145555556

03:01:53.600 --> 03:01:55.658 and that there's multiple potential factors,

NOTE Confidence: 0.733827145555556

03:01:55.660 --> 03:01:59.139 both in terms of urinary mineral excretion,

NOTE Confidence: 0.733827145555556

03:01:59.140 --> 03:01:59.990 dietary intake,

NOTE Confidence: 0.733827145555556

03:01:59.990 --> 03:02:02.115 and also vitamin D related.

NOTE Confidence: 0.733827145555556

03:02:02.120 --> 03:02:03.585 Minimum metabolism that play a

NOTE Confidence: 0.733827145555556

03:02:03.585 --> 03:02:05.446 role in the impaired bone quality

NOTE Confidence: 0.733827145555556

03:02:05.446 --> 03:02:06.786 in kidney stone disease.

NOTE Confidence: 0.779104722857143

03:02:11.240 --> 03:02:14.210 Finally, just I wanted to discuss

NOTE Confidence: 0.779104722857143

03:02:14.210 --> 03:02:16.190 cardiovascular complications of kidney

NOTE Confidence: 0.779104722857143

03:02:16.262 --> 03:02:18.932 stone disease and highlight what is

NOTE Confidence: 0.779104722857143

03:02:18.932 --> 03:02:21.774 currently a lack of data in children.

NOTE Confidence: 0.779104722857143

03:02:21.780 --> 03:02:24.065 So independent of other cardiovascular

NOTE Confidence: 0.779104722857143

03:02:24.065 --> 03:02:26.600 risk factors, several studies in

NOTE Confidence: 0.779104722857143

03:02:26.600 --> 03:02:28.990 adults have demonstrated kidney stones

NOTE Confidence: 0.779104722857143

03:02:28.990 --> 03:02:30.915 to be associated with hypertension.

NOTE Confidence: 0.779104722857143

03:02:30.920 --> 03:02:33.530 Arterial stiffness in the order

NOTE Confidence: 0.779104722857143

03:02:33.530 --> 03:02:35.096 calcification coronary disease,

NOTE Confidence: 0.779104722857143

03:02:35.100 --> 03:02:36.345 including myocardial infarction,

NOTE Confidence: 0.779104722857143

03:02:36.345 --> 03:02:38.005 stroke, and subclinical caretta

NOTE Confidence: 0.779104722857143

03:02:38.005 --> 03:02:39.789 that their sclerosis and young.

NOTE Confidence: 0.779104722857143

03:02:39.790 --> 03:02:41.282 Deals with kidney stones.

NOTE Confidence: 0.779104722857143

03:02:41.282 --> 03:02:43.558 And again, this excess myocardial infarction,

NOTE Confidence: 0.779104722857143

03:02:43.558 --> 03:02:45.850 which seemed to be more pronounced

NOTE Confidence: 0.779104722857143

03:02:45.912 --> 03:02:46.908 in younger adults.

NOTE Confidence: 0.779104722857143

03:02:46.910 --> 03:02:47.960 To my knowledge,

NOTE Confidence: 0.779104722857143

03:02:47.960 --> 03:02:50.060 there's still only one pediatric study

NOTE Confidence: 0.779104722857143

03:02:50.060 --> 03:02:52.461 that was done by Kirsten Kusumi looking

NOTE Confidence: 0.779104722857143

03:02:52.461 --> 03:02:54.669 at 15 adolescence with kidney stones.

NOTE Confidence: 0.779104722857143

03:02:54.670 --> 03:02:55.975 That showed that they had

NOTE Confidence: 0.779104722857143

03:02:55.975 --> 03:02:57.019 higher carotid intimal medial

NOTE Confidence: 0.779104722857143

03:02:57.019 --> 03:02:58.575 thickness compared to age, sex,

NOTE Confidence: 0.779104722857143

03:02:58.575 --> 03:03:02.205 and body mass index matched controls.

NOTE Confidence: 0.779104722857143

03:03:02.210 --> 03:03:04.365 So understanding the bone and

NOTE Confidence: 0.779104722857143

03:03:04.365 --> 03:03:05.658 vascular morbidity associated

NOTE Confidence: 0.779104722857143

03:03:05.658 --> 03:03:07.769 kidney stones is really important,

NOTE Confidence: 0.779104722857143

03:03:07.770 --> 03:03:09.840 particularly in our in our

NOTE Confidence: 0.779104722857143

03:03:09.840 --> 03:03:11.496 patient population that develops

NOTE Confidence: 0.779104722857143

03:03:11.496 --> 03:03:13.289 kidney stones early in life.

NOTE Confidence: 0.874584774666667

03:03:16.590 --> 03:03:19.158 So this brings me to another active study

NOTE Confidence: 0.874584774666667

03:03:19.158 --> 03:03:22.167 that we are close to completing enrollment.

NOTE Confidence: 0.874584774666667

03:03:22.170 --> 03:03:25.386 So target this is a prospective cohort study,

NOTE Confidence: 0.874584774666667

03:03:25.390 --> 03:03:27.707 just funded by our pediatric Center of

NOTE Confidence: 0.874584774666667

03:03:27.707 --> 03:03:29.392 Excellence and nephrology and target

NOTE Confidence: 0.874584774666667

03:03:29.392 --> 03:03:31.312 enrollment is 100 children and young

NOTE Confidence: 0.874584774666667

03:03:31.312 --> 03:03:33.070 adults between the ages of five and

NOTE Confidence: 0.874584774666667

03:03:33.070 --> 03:03:35.574 21 years of age with kidney stones.

NOTE Confidence: 0.874584774666667

03:03:35.574 --> 03:03:38.396 Primary outcomes are bone measures

NOTE Confidence: 0.874584774666667

03:03:38.396 --> 03:03:40.036 assessed by high resolution peripheral,

NOTE Confidence: 0.874584774666667

03:03:40.040 --> 03:03:42.260 quantitative computed tomography

NOTE Confidence: 0.874584774666667

03:03:42.260 --> 03:03:46.500 or HRCT as well as dexa.

NOTE Confidence: 0.874584774666667

03:03:46.500 --> 03:03:49.182 And participants are having these measures

NOTE Confidence: 0.874584774666667

03:03:49.182 --> 03:03:52.180 done at baseline and 12 to 24 months.

NOTE Confidence: 0.874584774666667

03:03:52.180 --> 03:03:55.836 We extended to 24 months because of COVID.

NOTE Confidence: 0.874584774666667

03:03:55.840 --> 03:03:57.808 They are also having 24 year,

NOTE Confidence: 0.874584774666667

03:03:57.810 --> 03:04:01.324 24 hour urine profiling and completing 324

NOTE Confidence: 0.874584774666667

03:04:01.324 --> 03:04:05.356 hour diet recalls at baseline and follow up.

NOTE Confidence: 0.874584774666667

03:04:05.360 --> 03:04:07.530 We were enrolling healthy controls

NOTE Confidence: 0.874584774666667

03:04:07.530 --> 03:04:09.700 and then because of COVID,

NOTE Confidence: 0.874584774666667

03:04:09.700 --> 03:04:10.930 I'm fortunate to be partnering

NOTE Confidence: 0.874584774666667

03:04:10.930 --> 03:04:12.500 with my mentor, Mary Leonard,

NOTE Confidence: 0.874584774666667

03:04:12.500 --> 03:04:14.575 who's been rolled over 200

NOTE Confidence: 0.874584774666667

03:04:14.580 --> 03:04:18.220 healthy participants at Stanford.

NOTE Confidence: 0.874584774666667

03:04:18.220 --> 03:04:20.430 Using the same second generation

NOTE Confidence: 0.874584774666667

03:04:20.430 --> 03:04:21.314 HRPC technology,

NOTE Confidence: 0.874584774666667

03:04:21.320 --> 03:04:24.840 so we are going to be comparing our

NOTE Confidence: 0.874584774666667

03:04:24.840 --> 03:04:26.920 population to that reference cohort

NOTE Confidence: 0.874584774666667

03:04:26.920 --> 03:04:29.507 because there are no normative values for

NOTE Confidence: 0.874584774666667

03:04:29.507 --> 03:04:31.810 HRPT and children as compared to Texas,

NOTE Confidence: 0.874584774666667

03:04:31.810 --> 03:04:33.760 where there are normative values

NOTE Confidence: 0.874584774666667

03:04:33.760 --> 03:04:36.080 and we can calculate Z scores.

NOTE Confidence: 0.613468171

03:04:39.140 --> 03:04:43.316 So just a word on HPCT.

NOTE Confidence: 0.613468171

03:04:43.320 --> 03:04:45.469 If this is a low radiation technology

NOTE Confidence: 0.613468171

03:04:45.469 --> 03:04:47.326 that provides measures of trabecular

NOTE Confidence: 0.613468171

03:04:47.326 --> 03:04:48.640 microarchitecture and cortical

NOTE Confidence: 0.613468171

03:04:48.640 --> 03:04:50.392 volumetric bone mineral density,

NOTE Confidence: 0.613468171

03:04:50.400 --> 03:04:51.510 porosity and structure,

NOTE Confidence: 0.613468171

03:04:51.510 --> 03:04:53.730 and therefore can really provide insight

NOTE Confidence: 0.613468171

03:04:53.730 --> 03:04:56.092 into the impact of disease effects on

NOTE Confidence: 0.613468171

03:04:56.092 --> 03:04:57.920 discrete components of bone strength.

NOTE Confidence: 0.613468171

03:04:57.920 --> 03:05:00.564 Additionally, HPCT through microfinance

NOTE Confidence: 0.613468171

03:05:00.564 --> 03:05:03.208 element analysis can actually

NOTE Confidence: 0.613468171

03:05:03.208 --> 03:05:05.939 provide indices of bone strength,

NOTE Confidence: 0.613468171

03:05:05.940 --> 03:05:07.851 and that one of those indices failure

NOTE Confidence: 0.613468171

03:05:07.851 --> 03:05:09.420 loads correlates well with xevil bio.

NOTE Confidence: 0.613468171

03:05:09.420 --> 03:05:11.100 Mechanical compression testing

NOTE Confidence: 0.613468171

03:05:11.100 --> 03:05:13.340 has provided good fracture

NOTE Confidence: 0.613468171

03:05:13.340 --> 03:05:15.819 discrimination in children and adults.

NOTE Confidence: 0.613468171

03:05:15.820 --> 03:05:16.153 Additionally,

NOTE Confidence: 0.613468171

03:05:16.153 --> 03:05:17.818 there's the potential to pick

NOTE Confidence: 0.613468171

03:05:17.818 --> 03:05:18.817 up vascular calcification,

NOTE Confidence: 0.613468171

03:05:18.820 --> 03:05:20.710 although we don't know if that's

NOTE Confidence: 0.613468171

03:05:20.710 --> 03:05:22.786 going to be possible in our

NOTE Confidence: 0.613468171

03:05:22.786 --> 03:05:24.656 pediatric and young adult population.

NOTE Confidence: 0.791374275111111

03:05:30.300 --> 03:05:31.410 So to summarize,

NOTE Confidence: 0.791374275111111

03:05:31.410 --> 03:05:33.630 kidney stone disease is highly prevalent,

NOTE Confidence: 0.791374275111111

03:05:33.630 --> 03:05:36.472 and on the rise and the rising

NOTE Confidence: 0.791374275111111

03:05:36.472 --> 03:05:37.690 incidence is disproportionately

NOTE Confidence: 0.791374275111111

03:05:37.761 --> 03:05:39.857 affecting adolescents and women.

NOTE Confidence: 0.791374275111111

03:05:39.860 --> 03:05:41.540 There's growing evidence for display.

NOTE Confidence: 0.791374275111111

03:05:41.540 --> 03:05:43.640 Osis is a potential mediator

NOTE Confidence: 0.791374275111111

03:05:43.640 --> 03:05:46.268 for this changing incidents.

NOTE Confidence: 0.791374275111111

03:05:46.270 --> 03:05:48.230 An increasing recognition of associated

NOTE Confidence: 0.791374275111111

03:05:48.230 --> 03:05:50.190 morbidity and long-term renal and

NOTE Confidence: 0.791374275111111

03:05:50.251 --> 03:05:52.506 extrarenal complications of kidney stones.

NOTE Confidence: 0.791374275111111

03:05:52.510 --> 03:05:55.184 And again, this is a particular concern

NOTE Confidence: 0.791374275111111

03:05:55.184 --> 03:05:57.474 with earlier onset disease and what

NOTE Confidence: 0.791374275111111

03:05:57.474 --> 03:05:59.622 this means over the life course.

NOTE Confidence: 0.791374275111111

03:05:59.630 --> 03:06:03.174 So our current work is really focused on

NOTE Confidence: 0.791374275111111

03:06:03.174 --> 03:06:05.100 delineating mechanistic underpinnings.

NOTE Confidence: 0.791374275111111

03:06:05.100 --> 03:06:07.242 About the about the origins and

NOTE Confidence: 0.791374275111111

03:06:07.242 --> 03:06:09.073 complications of kidney stones so

NOTE Confidence: 0.791374275111111

03:06:09.073 --> 03:06:11.143 that we can improve both primary

NOTE Confidence: 0.791374275111111

03:06:11.143 --> 03:06:12.997 and secondary prevention of kidney

NOTE Confidence: 0.791374275111111

03:06:12.997 --> 03:06:14.887 stone disease and its complications.

NOTE Confidence: 0.791374275111111

03:06:14.890 --> 03:06:17.794 I just want to thank all of the members

NOTE Confidence: 0.791374275111111

03:06:17.794 --> 03:06:19.978 of the research teams that worked

NOTE Confidence: 0.791374275111111

03:06:19.978 --> 03:06:22.686 on the the settings that are that

NOTE Confidence: 0.791374275111111

03:06:22.686 --> 03:06:25.458 I presented that are ongoing and my

NOTE Confidence: 0.791374275111111

03:06:25.458 --> 03:06:27.768 partner Greg Tatian in urology Tub

NOTE Confidence: 0.791374275111111

03:06:27.768 --> 03:06:30.778 who's really been my Co Pi in all of

NOTE Confidence: 0.791374275111111

03:06:30.778 --> 03:06:33.469 this work and our funding sources.

NOTE Confidence: 0.791374275111111

03:06:33.470 --> 03:06:34.590 Thank you very much.

NOTE Confidence: 0.767553482

03:06:48.300 --> 03:06:49.740 Thanks for a wonderful talk.

NOTE Confidence: 0.767553482

03:06:49.740 --> 03:06:51.430 Any questions for doctor Denver?

NOTE Confidence: 0.22355655

03:06:54.590 --> 03:06:54.860 Ever.

NOTE Confidence: 0.888344195714286

03:07:16.000 --> 03:07:17.827 Are you able to hear that or?

NOTE Confidence: 0.888344195714286

03:07:17.830 --> 03:07:21.154 I did not. I'm so sorry to repeat it.

NOTE Confidence: 0.888344195714286

03:07:21.154 --> 03:07:22.706 I think she's on.

NOTE Confidence: 0.888344195714286

03:07:22.710 --> 03:07:25.658 Julie Goodwin sees babies later

NOTE Confidence: 0.888344195714286

03:07:25.658 --> 03:07:28.022 six months old with the kidney

NOTE Confidence: 0.888344195714286

03:07:28.022 --> 03:07:30.924 stones and is it due to potentially

NOTE Confidence: 0.888344195714286

03:07:30.924 --> 03:07:32.964 from formula or antibiotic use?

NOTE Confidence: 0.888344195714286

03:07:32.970 --> 03:07:36.230 Or what's the potential ideology?

NOTE Confidence: 0.888344195714286

03:07:36.230 --> 03:07:37.854 That's I think that's a great question.

NOTE Confidence: 0.888344195714286

03:07:37.860 --> 03:07:41.100 I think the work that we're doing right now,

NOTE Confidence: 0.888344195714286

03:07:41.100 --> 03:07:42.556 you know, we we are not enrolling

NOTE Confidence: 0.888344195714286

03:07:42.556 --> 03:07:43.796 anybody that young, but it's.

NOTE Confidence: 0.888344195714286

03:07:43.796 --> 03:07:45.644 It's a good question whether we

NOTE Confidence: 0.888344195714286

03:07:45.644 --> 03:07:47.397 should consider it a new direction

NOTE Confidence: 0.888344195714286

03:07:47.397 --> 03:07:50.690 and because you know, I think.

NOTE Confidence: 0.888344195714286

03:07:50.690 --> 03:07:52.610 Particularly for some of the kidney

NOTE Confidence: 0.888344195714286

03:07:52.610 --> 03:07:54.420 stones we see early in life.

NOTE Confidence: 0.888344195714286

03:07:54.420 --> 03:07:56.898 You know, particularly in the NICU.

NOTE Confidence: 0.888344195714286

03:07:56.900 --> 03:07:58.300 So I think it's a great question

NOTE Confidence: 0.888344195714286

03:07:58.300 --> 03:07:59.719 and a great future direction,

NOTE Confidence: 0.888344195714286

03:07:59.720 --> 03:08:02.426 and we are really hoping to

NOTE Confidence: 0.888344195714286

03:08:02.426 --> 03:08:04.878 delve into the dietary influences

NOTE Confidence: 0.888344195714286

03:08:04.878 --> 03:08:07.658 in the ongoing poop study.

NOTE Confidence: 0.888344195714286

03:08:07.660 --> 03:08:10.824 But we don't have anybody that young.

NOTE Confidence: 0.888344195714286

03:08:10.830 --> 03:08:11.140 Alright.

NOTE Confidence: 0.45955837

03:08:25.880 --> 03:08:26.380 More more.

NOTE Confidence: 0.3744582

03:08:30.370 --> 03:08:30.740 However.

NOTE Confidence: 0.92033552

03:08:44.560 --> 03:08:48.865 So can you modulate the aux light content

NOTE Confidence: 0.92033552

03:08:48.865 --> 03:08:53.600 by by the diet or increasing your calcium

NOTE Confidence: 0.92033552

03:08:53.600 --> 03:08:57.296 to change also the the microbiome?

NOTE Confidence: 0.92033552

03:08:57.300 --> 03:08:58.800 Yeah, I think we don't know.

NOTE Confidence: 0.92033552

03:08:58.800 --> 03:09:00.968 We don't know yet, but I think that

NOTE Confidence: 0.92033552

03:09:00.968 --> 03:09:03.259 is the idea that you know can we?

NOTE Confidence: 0.92033552

03:09:03.260 --> 03:09:06.725 What can we learn that can help both with

NOTE Confidence: 0.92033552

03:09:06.725 --> 03:09:09.926 primary but even secondary prevention for

NOTE Confidence: 0.92033552

03:09:09.926 --> 03:09:13.436 recurrent stone farmers by manipulating?

NOTE Confidence: 0.92033552

03:09:13.440 --> 03:09:15.508 Might be manipulating diet

NOTE Confidence: 0.92033552

03:09:15.508 --> 03:09:17.576 to change the microbiome.

NOTE Confidence: 0.92033552

03:09:17.580 --> 03:09:19.422 I think that is where, where,

NOTE Confidence: 0.92033552

03:09:19.422 --> 03:09:22.194 where this work is hopefully heading.

NOTE Confidence: 0.92033552

03:09:22.200 --> 03:09:25.216 Is this also like important in like uric

NOTE Confidence: 0.92033552

03:09:25.216 --> 03:09:27.856 acid stones or other forms of stones?

NOTE Confidence: 0.92033552

03:09:27.860 --> 03:09:30.555 Or is it just for calcium oxalate?

NOTE Confidence: 0.92033552

03:09:30.560 --> 03:09:31.876 That's a good question. I mean I'm.

NOTE Confidence: 0.92033552

03:09:31.880 --> 03:09:33.698 I mean it, it could be.

NOTE Confidence: 0.92033552

03:09:33.700 --> 03:09:37.040 I mean the our work and the the body of

NOTE Confidence: 0.92033552

03:09:37.130 --> 03:09:40.847 literature that I'm familiar with is really

NOTE Confidence: 0.92033552

03:09:40.847 --> 03:09:43.656 focused on calcium based kidney stones.

NOTE Confidence: 0.92033552

03:09:43.656 --> 03:09:44.700 And you know,

NOTE Confidence: 0.92033552

03:09:44.700 --> 03:09:48.020 there's been a lot of attention to oxalate

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NOTE Confidence: 0.92033552

03:09:48.020 --> 03:09:51.646 and the effect of the microbiome on Oxley,

NOTE Confidence: 0.92033552

03:09:51.646 --> 03:09:55.354 but I think that's why we really wanted to

NOTE Confidence: 0.92033552

03:09:55.354 --> 03:09:57.960 take a more agnostic approach to looking

NOTE Confidence: 0.92033552

03:09:57.960 --> 03:10:00.360 at the urine chemistries more broadly,

NOTE Confidence: 0.92033552

03:10:00.360 --> 03:10:01.400 the interaction.

NOTE Confidence: 0.92033552

03:10:01.400 --> 03:10:04.000 Between external exposures and microbiome

NOTE Confidence: 0.92033552

03:10:04.000 --> 03:10:05.992 and urine chemistries more broadly,

NOTE Confidence: 0.92033552

03:10:05.992 --> 03:10:07.288 but we we are not looking,

NOTE Confidence: 0.92033552

03:10:07.290 --> 03:10:09.070 we we have specifically excluded

NOTE Confidence: 0.92033552

03:10:09.070 --> 03:10:11.340 your against the uric acid stones.

NOTE Confidence: 0.92033552

03:10:11.340 --> 03:10:12.575 From our analysis and they're

NOTE Confidence: 0.92033552

03:10:12.575 --> 03:10:13.563 very rare in childhood.

NOTE Confidence: 0.920246833333333

03:10:18.240 --> 03:10:19.320 Any other questions?

NOTE Confidence: 0.758471814375

03:10:22.260 --> 03:10:23.900 Thank you Doctor Dembrow for a great talk.

NOTE Confidence: 0.874213148333333

03:10:29.050 --> 03:10:33.910 So we'll reconvene after lunch at 1:00 PM,

NOTE Confidence: 0.874213148333333

03:10:33.910 --> 03:10:36.764 thanks. All right, I think we can

NOTE Confidence: 0.874213148333333

03:10:36.764 --> 03:10:38.729 get started with our last speaker,

NOTE Confidence: 0.874213148333333

03:10:38.730 --> 03:10:43.110 doctor Opeyemi Olabisi from.

NOTE Confidence: 0.874213148333333

03:10:43.110 --> 03:10:45.990 Duke Health who's going to talk to us about

NOTE Confidence: 0.874213148333333

03:10:45.990 --> 03:10:47.668 translational insights from patients.

NOTE Confidence: 0.874213148333333

03:10:47.670 --> 03:10:51.336 Stem cell derived model of April

NOTE Confidence: 0.874213148333333

03:10:51.336 --> 03:10:54.840 1 nephropathy. Thank you Amy.

NOTE Confidence: 0.874213148333333

03:10:54.840 --> 03:10:56.584 Thank you very much,

NOTE Confidence: 0.874213148333333

03:10:56.584 --> 03:10:59.195 Doctor Ishibe and thank you to the

NOTE Confidence: 0.874213148333333

03:10:59.195 --> 03:11:01.799 organizer and Doctor Shebib for inviting me.

NOTE Confidence: 0.874213148333333

03:11:01.800 --> 03:11:06.070 I'm quite honored to this.

NOTE Confidence: 0.874213148333333

03:11:06.070 --> 03:11:08.563 Symposium I wish I could be there in person,

NOTE Confidence: 0.874213148333333

03:11:08.570 --> 03:11:10.076 but different scheduling

NOTE Confidence: 0.874213148333333

03:11:10.076 --> 03:11:12.084 issues that prevents me,

NOTE Confidence: 0.874213148333333

03:11:12.090 --> 03:11:14.295 so I'm quite excited to be here.

NOTE Confidence: 0.874213148333333

03:11:14.300 --> 03:11:16.430 The morning session was quite enjoyable

NOTE Confidence: 0.874213148333333

03:11:16.430 --> 03:11:18.450 listening to all the speakers,

NOTE Confidence: 0.874213148333333

03:11:18.450 --> 03:11:20.988 including Doctor, Babbitt and Doctor Roses,

NOTE Confidence: 0.874213148333333

03:11:20.990 --> 03:11:24.110 and all, so it's been very exciting day,

NOTE Confidence: 0.874213148333333

03:11:24.110 --> 03:11:25.606 and I know this is the last talk,

NOTE Confidence: 0.874213148333333

03:11:25.610 --> 03:11:28.634 so I hope you actually will enjoy it also.

NOTE Confidence: 0.821564489333333

03:11:32.040 --> 03:11:34.735 So none of the conflict is really

NOTE Confidence: 0.821564489333333

03:11:34.735 --> 03:11:37.857 relevant to the talk I'm be given today,

NOTE Confidence: 0.821564489333333

03:11:37.860 --> 03:11:40.440 and I usually do not forget.

NOTE Confidence: 0.821564489333333

03:11:40.440 --> 03:11:43.416 I want to kind of give credit to

NOTE Confidence: 0.821564489333333

03:11:43.416 --> 03:11:46.409 people who actually did all the work

NOTE Confidence: 0.821564489333333

03:11:46.409 --> 03:11:49.734 and Doctor George Lee is a postdoc in

NOTE Confidence: 0.821564489333333

03:11:49.734 --> 03:11:52.900 the lab to the left, Sarah Nystrom.

NOTE Confidence: 0.821564489333333

03:11:52.900 --> 03:11:58.420 Is nephrology rising star fellow in the lab.

NOTE Confidence: 0.821564489333333

03:11:58.420 --> 03:11:59.806 Is the first author of the paper

NOTE Confidence: 0.821564489333333

03:11:59.806 --> 03:12:01.149 that they'll be presenting later.

NOTE Confidence: 0.821564489333333

03:12:01.150 --> 03:12:05.210 Deraya minor is my clinical

NOTE Confidence: 0.821564489333333

03:12:05.210 --> 03:12:06.834 research coordinator.

NOTE Confidence: 0.821564489333333

03:12:06.840 --> 03:12:08.568 With the subnet data,

NOTE Confidence: 0.821564489333333

03:12:08.568 --> 03:12:11.925 I suppose duck Daniel Silers is the research

NOTE Confidence: 0.821564489333333

03:12:11.925 --> 03:12:15.409 tech in the lab and carries soldano.

NOTE Confidence: 0.821564489333333

03:12:15.410 --> 03:12:17.444 Is my lab manager without them

NOTE Confidence: 0.821564489333333

03:12:17.444 --> 03:12:19.650 all this stuff I'll be talking

NOTE Confidence: 0.821564489333333

03:12:19.650 --> 03:12:21.590 about today would not happen,

NOTE Confidence: 0.821564489333333

03:12:21.590 --> 03:12:24.166 so they get the front row seat.

NOTE Confidence: 0.821564489333333

03:12:24.170 --> 03:12:28.460 So my goal today is to.

NOTE Confidence: 0.821564489333333

03:12:28.460 --> 03:12:30.136 Go through this overview.

NOTE Confidence: 0.821564489333333

03:12:30.136 --> 03:12:32.650 Some of them are familiar but

NOTE Confidence: 0.821564489333333

03:12:32.734 --> 03:12:35.098 also couch this in two stories.

NOTE Confidence: 0.821564489333333

03:12:35.100 --> 03:12:37.242 One of them just recently published

NOTE Confidence: 0.821564489333333

03:12:37.242 --> 03:12:39.960 and the other one is still emerging.

NOTE Confidence: 0.821564489333333

03:12:39.960 --> 03:12:41.259 To highlight this,

03:12:41.259 --> 03:12:43.857 the use of patient derived IPS

03:12:43.857 --> 03:12:46.660 model as a way of studying disease.

03:12:46.660 --> 03:12:49.588 I will go over the high burden of

03:12:49.588 --> 03:12:52.238 kidney disease among African Americans.

03:12:52.240 --> 03:12:54.160 Factors that contribute especially

03:12:54.160 --> 03:12:56.560 biological factors that will be

03:12:56.560 --> 03:12:59.320 discussing today the role of experimental.

03:12:59.320 --> 03:13:02.170 Models in understanding the role of

03:13:02.249 --> 03:13:05.325 equal 1 and also I will be ending by

03:13:05.325 --> 03:13:07.850 transitioning to once we actually

03:13:07.850 --> 03:13:11.200 understand the the mechanism and and whatnot.

03:13:11.200 --> 03:13:13.376 How do we translate this to the community?

03:13:13.380 --> 03:13:16.402 How do we overcome barriers that have

03:13:16.402 --> 03:13:18.457 prevented translations in the past,

03:13:18.460 --> 03:13:20.764 and I'll be introducing a care

03:13:20.764 --> 03:13:23.228 and justice and NIH funded program

NOTE Confidence: 0.821564489333333

03:13:23.228 --> 03:13:24.920 that we are doing.

NOTE Confidence: 0.821564489333333

03:13:24.920 --> 03:13:28.016 Many of you may be familiar with this book.

NOTE Confidence: 0.821564489333333

03:13:28.020 --> 03:13:29.970 It it's called the warmth of

NOTE Confidence: 0.821564489333333

03:13:29.970 --> 03:13:32.000 other Suns by Isabel Wilkerson.

NOTE Confidence: 0.821564489333333

03:13:32.000 --> 03:13:32.732 I really,

NOTE Confidence: 0.821564489333333

03:13:32.732 --> 03:13:35.294 really enjoyed the book on many level.

NOTE Confidence: 0.821564489333333

03:13:35.300 --> 03:13:37.400 It chronicled the great Migration,

NOTE Confidence: 0.821564489333333

03:13:37.400 --> 03:13:40.640 the migration of about 6 million

NOTE Confidence: 0.821564489333333

03:13:40.640 --> 03:13:43.296 African Americans between 1915 to

NOTE Confidence: 0.821564489333333

03:13:43.296 --> 03:13:46.922 1970 from the South to the north

NOTE Confidence: 0.821564489333333

03:13:46.922 --> 03:13:49.558 and also to the West.

NOTE Confidence: 0.821564489333333

03:13:49.560 --> 03:13:53.130 The book is the author interview

NOTE Confidence: 0.821564489333333

03:13:53.130 --> 03:13:55.510 like maybe 1000 individuals.

NOTE Confidence: 0.821564489333333

03:13:55.510 --> 03:13:58.546 Pretty much is very nice book.

NOTE Confidence: 0.821564489333333

03:13:58.550 --> 03:14:00.066 But in the subtext,

03:14:00.066 --> 03:14:03.419 or let me say she followed 3 characters

03:14:03.420 --> 03:14:05.065 as a way of telling this story,

03:14:05.070 --> 03:14:06.790 throw you real human characters,

03:14:06.790 --> 03:14:07.492 African Americans.

03:14:07.492 --> 03:14:09.949 This is the movement of African Americans

03:14:09.949 --> 03:14:12.088 from the South to the north and West.

03:14:12.090 --> 03:14:13.308 Three of them, one of them,

03:14:13.310 --> 03:14:15.230 actually ended up going West.

03:14:15.230 --> 03:14:18.044 He became the the personal physician

03:14:18.044 --> 03:14:21.030 to to the musician Ray Charles,

03:14:21.030 --> 03:14:22.470 of the three characters.

03:14:22.470 --> 03:14:23.190 She followed.

03:14:23.190 --> 03:14:26.179 Two of them died with kidney failure.

03:14:26.180 --> 03:14:26.411 So,

03:14:26.411 --> 03:14:28.259 and this is where I'm going with this.

03:14:28.260 --> 03:14:30.852 Even when you look historically into

NOTE Confidence: 0.821564489333333

03:14:30.852 --> 03:14:33.298 the African American history here you

NOTE Confidence: 0.821564489333333

03:14:33.298 --> 03:14:35.573 see that the the higher burden of

NOTE Confidence: 0.821564489333333

03:14:35.573 --> 03:14:38.410 kidney failure is not something new, it's a.

NOTE Confidence: 0.821564489333333

03:14:38.410 --> 03:14:39.940 It's a kidney failure that's been.

NOTE Confidence: 0.821564489333333

03:14:39.940 --> 03:14:43.414 And it's not a new problem in this community.

NOTE Confidence: 0.821564489333333

03:14:43.420 --> 03:14:45.555 And as you many of you know,

NOTE Confidence: 0.821564489333333

03:14:45.560 --> 03:14:48.368 in the audience that African American

NOTE Confidence: 0.821564489333333

03:14:48.368 --> 03:14:51.288 constitute 13% of US population,

NOTE Confidence: 0.821564489333333

03:14:51.288 --> 03:14:54.080 but 35% of patients on dialysis.

NOTE Confidence: 0.821564489333333

03:14:54.080 --> 03:14:55.718 And we know that the burden

NOTE Confidence: 0.821564489333333

03:14:55.718 --> 03:14:56.537 of kidney disease.

NOTE Confidence: 0.821564489333333

03:14:56.540 --> 03:14:58.575 The incidence of end stage

NOTE Confidence: 0.821564489333333

03:14:58.575 --> 03:15:00.610 kidney disease among blacks is

NOTE Confidence: 0.857563268235294

03:15:00.685 --> 03:15:03.394 at four times higher than among white.

NOTE Confidence: 0.857563268235294

03:15:03.400 --> 03:15:05.812 The risk is higher in other groups as well.

NOTE Confidence: 0.857563268235294

03:15:05.820 --> 03:15:08.361 You see the Spanish and the Native

NOTE Confidence: 0.857563268235294

03:15:08.361 --> 03:15:10.316 American Hispanics and the Asian

NOTE Confidence: 0.857563268235294

03:15:10.316 --> 03:15:12.316 relative to to European Americans.

NOTE Confidence: 0.857563268235294

03:15:12.320 --> 03:15:16.352 But focusing on African American this in this

NOTE Confidence: 0.857563268235294

03:15:16.352 --> 03:15:19.476 conversation the risk is full fold higher,

NOTE Confidence: 0.857563268235294

03:15:19.480 --> 03:15:22.618 and this risk actually has consequences.

NOTE Confidence: 0.857563268235294

03:15:22.620 --> 03:15:24.853 Here I listed some of the the

NOTE Confidence: 0.857563268235294

03:15:24.853 --> 03:15:27.119 the the reason why this problem.

NOTE Confidence: 0.857563268235294

03:15:27.120 --> 03:15:29.676 OK, kidney disease is very care.

NOTE Confidence: 0.857563268235294

03:15:29.680 --> 03:15:31.072 Failure is very deadly.

NOTE Confidence: 0.857563268235294

03:15:31.072 --> 03:15:32.812 I'm talking to many nephrologists

NOTE Confidence: 0.857563268235294

03:15:32.812 --> 03:15:33.840 this is no news.

NOTE Confidence: 0.857563268235294

03:15:33.840 --> 03:15:36.042 I mentioned it's an equal opportunity

NOTE Confidence: 0.857563268235294

03:15:36.042 --> 03:15:38.569 offender and it cost a lot of money

NOTE Confidence: 0.857563268235294

03:15:38.569 --> 03:15:40.915 and one of the fact that I found that

NOTE Confidence: 0.857563268235294

03:15:40.915 --> 03:15:43.554 just in my mind study is when you look

NOTE Confidence: 0.857563268235294

03:15:43.554 --> 03:15:45.876 at the epidemiology of kidney failure,

NOTE Confidence: 0.857563268235294

03:15:45.880 --> 03:15:46.951 black men's life,

NOTE Confidence: 0.857563268235294

03:15:46.951 --> 03:15:49.093 lost to kidney failure is similar

NOTE Confidence: 0.857563268235294

03:15:49.093 --> 03:15:51.507 to life lost to colon cancer and

NOTE Confidence: 0.857563268235294

03:15:51.507 --> 03:15:53.301 for black women it's similar to

NOTE Confidence: 0.857563268235294

03:15:53.301 --> 03:15:54.636 life loss to breast cancer.

NOTE Confidence: 0.857563268235294

03:15:54.640 --> 03:15:56.878 So a lot is quite deadly.

NOTE Confidence: 0.857563268235294

03:15:56.880 --> 03:15:58.130 And what causes this is,

NOTE Confidence: 0.857563268235294

03:15:58.130 --> 03:15:59.898 you know many factors.

NOTE Confidence: 0.857563268235294

03:15:59.898 --> 03:16:02.920 I think I believe the last two

NOTE Confidence: 0.857563268235294

03:16:02.920 --> 03:16:05.643 two year plus as I lighted the

NOTE Confidence: 0.857563268235294

03:16:05.643 --> 03:16:07.612 contribution of non biological

NOTE Confidence: 0.857563268235294

03:16:07.612 --> 03:16:10.480 factor including structural racism,

NOTE Confidence: 0.857563268235294

03:16:10.480 --> 03:16:12.256 socioeconomic factors and environment.

NOTE Confidence: 0.857563268235294

03:16:12.256 --> 03:16:15.301 But then there's also biology which is

NOTE Confidence: 0.857563268235294

03:16:15.301 --> 03:16:17.485 indisputable and this is where it will

NOTE Confidence: 0.857563268235294

03:16:17.485 --> 03:16:20.156 won't fall in that I'll be discussing today.

NOTE Confidence: 0.857563268235294

03:16:20.160 --> 03:16:23.286 Many of you know that in 2010 Doctor

NOTE Confidence: 0.857563268235294

03:16:23.286 --> 03:16:26.724 Pollack my my mentor in Boston.

NOTE Confidence: 0.857563268235294

03:16:26.730 --> 03:16:30.054 By Chinese group and many others

NOTE Confidence: 0.857563268235294

03:16:30.054 --> 03:16:32.270 collaborating together identify that

NOTE Confidence: 0.857563268235294

03:16:32.357 --> 03:16:35.087 polymorphisms in the equal 1 gene,

NOTE Confidence: 0.857563268235294

03:16:35.090 --> 03:16:37.866 illustrated as a cartoon here account

NOTE Confidence: 0.857563268235294

03:16:37.866 --> 03:16:40.568 for a high burden of kidney disease

NOTE Confidence: 0.857563268235294

03:16:40.568 --> 03:16:42.611 among people of recent African

NOTE Confidence: 0.857563268235294

03:16:42.611 --> 03:16:45.011 ancestry and the story that unfolded

NOTE Confidence: 0.857563268235294

03:16:45.011 --> 03:16:47.292 was that the reference, if well,

NOTE Confidence: 0.857563268235294

03:16:47.292 --> 03:16:49.049 when the wild type is the G0,

NOTE Confidence: 0.857563268235294

03:16:49.050 --> 03:16:50.028 shown here,

NOTE Confidence: 0.857563268235294

03:16:50.028 --> 03:16:53.451 G1 and G2 evolve around 4 to

NOTE Confidence: 0.857563268235294

03:16:53.451 --> 03:16:56.778 6000 years ago in West Africa.

NOTE Confidence: 0.857563268235294

03:16:56.780 --> 03:16:59.642 Where G1 I resulted from serine

NOTE Confidence: 0.857563268235294

03:16:59.642 --> 03:17:01.073 to glycine substitution,

NOTE Confidence: 0.857563268235294

03:17:01.080 --> 03:17:03.296 isoleucine to methionine substitution.

NOTE Confidence: 0.857563268235294

03:17:03.296 --> 03:17:06.620 This mutation almost always occurs together

NOTE Confidence: 0.857563268235294

03:17:06.696 --> 03:17:09.200 and then G2 is 2 amino acid deletion.

NOTE Confidence: 0.857563268235294

03:17:09.200 --> 03:17:12.455 In this Sr a domain and it appears

NOTE Confidence: 0.857563268235294

03:17:12.455 --> 03:17:14.235 that the evolutionary benefits

NOTE Confidence: 0.857563268235294

03:17:14.235 --> 03:17:17.489 of having G1 or G2 is protection

NOTE Confidence: 0.857563268235294

03:17:17.489 --> 03:17:19.329 from the African trypanosome

NOTE Confidence: 0.857563268235294

03:17:19.329 --> 03:17:22.020 parasite in Ethereum zygote state.

NOTE Confidence: 0.857563268235294

03:17:22.020 --> 03:17:25.420 But when you have two copies in homozygous

NOTE Confidence: 0.857563268235294

03:17:25.420 --> 03:17:27.929 or compound that they're almost.

NOTE Confidence: 0.857563268235294

03:17:27.930 --> 03:17:31.170 IG1G1 or G1G2 or G2G2.

NOTE Confidence: 0.857563268235294

03:17:31.170 --> 03:17:33.508 It increases the risk of kidney disease,

NOTE Confidence: 0.857563268235294

03:17:33.510 --> 03:17:35.911 So what nature gave with one hand

NOTE Confidence: 0.857563268235294

03:17:35.911 --> 03:17:38.667 he took away with the other and we

NOTE Confidence: 0.857563268235294

03:17:38.667 --> 03:17:41.370 know that 400 years ago with the

NOTE Confidence: 0.857563268235294

03:17:41.370 --> 03:17:43.410 with the transatlantic slave trade,

NOTE Confidence: 0.857563268235294

03:17:43.410 --> 03:17:45.150 this gene came to the Americas,

NOTE Confidence: 0.857563268235294

03:17:45.150 --> 03:17:47.870 not just the United States but also to

NOTE Confidence: 0.857563268235294

03:17:47.870 --> 03:17:49.988 South America and to the Caribbean.

NOTE Confidence: 0.857563268235294

03:17:49.990 --> 03:17:52.510 Why is this genome present in European?

NOTE Confidence: 0.857563268235294

03:17:52.510 --> 03:17:54.544 Because the out of Africa migration

NOTE Confidence: 0.857563268235294

03:17:54.544 --> 03:17:56.270 to Europe are called long,

NOTE Confidence: 0.857563268235294

03:17:56.270 --> 03:17:58.302 long before 2200 thousand.

NOTE Confidence: 0.857563268235294

03:17:58.302 --> 03:18:00.842 Musical before April 1 emerge

NOTE Confidence: 0.857563268235294

03:18:00.842 --> 03:18:02.240 around 4 to 6000.

NOTE Confidence: 0.857563268235294

03:18:02.240 --> 03:18:07.092 Years before so we now know that among

NOTE Confidence: 0.857563268235294

03:18:07.092 --> 03:18:09.000 African Americans anywhere between

NOTE Confidence: 0.857563268235294

03:18:09.082 --> 03:18:12.786 10 to 15% of blacks have to risk

NOTE Confidence: 0.857563268235294

03:18:12.786 --> 03:18:14.721 halilovic poelma that's shown here.

NOTE Confidence: 0.857563268235294

03:18:14.721 --> 03:18:16.383 So I'll be referring to this

NOTE Confidence: 0.857563268235294

03:18:16.383 --> 03:18:17.887 as high as the genotype,

NOTE Confidence: 0.857563268235294

03:18:17.890 --> 03:18:20.422 but there have been cases where

NOTE Confidence: 0.857563268235294

03:18:20.422 --> 03:18:22.110 impatient with kidney disease,

NOTE Confidence: 0.80177862625

03:18:22.110 --> 03:18:25.230 when we biopsy them and we genotype them,

NOTE Confidence: 0.80177862625

03:18:25.230 --> 03:18:27.438 there are some self identified white

NOTE Confidence: 0.80177862625

03:18:27.438 --> 03:18:29.241 individual, especially some self.

NOTE Confidence: 0.80177862625

03:18:29.241 --> 03:18:31.804 Identify why this panics that also

NOTE Confidence: 0.80177862625

03:18:31.804 --> 03:18:33.439 carry this high risk genotype.

NOTE Confidence: 0.80177862625

03:18:33.440 --> 03:18:34.756 What does that mean?

NOTE Confidence: 0.80177862625

03:18:34.756 --> 03:18:37.810 It means that in the lineage of that person,

NOTE Confidence: 0.80177862625

03:18:37.810 --> 03:18:40.330 that person have recent African ancestry,

NOTE Confidence: 0.80177862625

03:18:40.330 --> 03:18:42.990 so it's not totally accurate.

NOTE Confidence: 0.80177862625

03:18:42.990 --> 03:18:44.856 In fact, it may be misleading

NOTE Confidence: 0.80177862625

03:18:44.856 --> 03:18:47.114 to think of high risk of well

NOTE Confidence: 0.80177862625

03:18:47.114 --> 03:18:49.004 one genotype as a race issue.

NOTE Confidence: 0.80177862625

03:18:49.010 --> 03:18:50.900 In fact, it's an ancestry issue.

NOTE Confidence: 0.80177862625

03:18:50.900 --> 03:18:52.010 There was a question before.

NOTE Confidence: 0.80177862625

03:18:52.010 --> 03:18:53.338 How do you distinguish

NOTE Confidence: 0.80177862625

03:18:53.338 --> 03:18:54.666 between ancestry and race?

NOTE Confidence: 0.80177862625

03:18:54.670 --> 03:18:57.030 The best way to think of this risk

NOTE Confidence: 0.80177862625

03:18:57.030 --> 03:18:59.427 allele is it reflect recent African.

NOTE Confidence: 0.80177862625

03:18:59.430 --> 03:19:02.685 Necessary now is it just a

NOTE Confidence: 0.80177862625

03:19:02.685 --> 03:19:04.700 risk factor or is it causal?

NOTE Confidence: 0.80177862625

03:19:04.700 --> 03:19:06.360 Driver of disease work

NOTE Confidence: 0.80177862625

03:19:06.360 --> 03:19:08.020 from Catalan zuster club.

NOTE Confidence: 0.80177862625

03:19:08.020 --> 03:19:10.612 I think she she was the first to make

NOTE Confidence: 0.80177862625

03:19:10.612 --> 03:19:13.053 a mouse model that actually depicted

NOTE Confidence: 0.80177862625

03:19:13.053 --> 03:19:16.205 this where she made a mouse model that

NOTE Confidence: 0.80177862625

03:19:16.205 --> 03:19:19.172 X Ray said that Jezero G1 or G2 equal

NOTE Confidence: 0.80177862625

03:19:19.172 --> 03:19:21.700 1 you recall that G0 is a reference,

NOTE Confidence: 0.80177862625

03:19:21.700 --> 03:19:24.136 the wildtype G1 and G2 at

NOTE Confidence: 0.80177862625

03:19:24.136 --> 03:19:26.380 the risk alleles now miles.

NOTE Confidence: 0.80177862625

03:19:26.380 --> 03:19:28.222 I'm pretty much all of all

NOTE Confidence: 0.80177862625

03:19:28.222 --> 03:19:29.450 of our experimental animal.

NOTE Confidence: 0.80177862625

03:19:29.450 --> 03:19:32.422 There's like a poor one normally,

NOTE Confidence: 0.80177862625

03:19:32.422 --> 03:19:34.326 so mouse doesn't have a Powell one.

NOTE Confidence: 0.80177862625

03:19:34.330 --> 03:19:36.866 So to study it you have to do

NOTE Confidence: 0.80177862625

03:19:36.866 --> 03:19:38.589 transition generated transgenic mice.

NOTE Confidence: 0.80177862625

03:19:38.590 --> 03:19:40.165 She demonstrated that these mice

NOTE Confidence: 0.80177862625

03:19:40.165 --> 03:19:41.425 actually have kidney disease,

NOTE Confidence: 0.80177862625

03:19:41.430 --> 03:19:43.954 as indicated by proteinuria,

NOTE Confidence: 0.80177862625

03:19:43.954 --> 03:19:45.847 elevated BUN creatinine,

NOTE Confidence: 0.80177862625

03:19:45.850 --> 03:19:47.314 and when you look at their

NOTE Confidence: 0.80177862625

03:19:47.314 --> 03:19:48.290 kidney they also has.

NOTE Confidence: 0.80177862625

03:19:48.290 --> 03:19:50.680 They also have sclerosis that

03:19:50.680 --> 03:19:53.670 phenocopies what we see in human.

03:19:53.670 --> 03:19:56.295 My mentor in Boston doctor Pollack I

03:19:56.295 --> 03:19:58.504 wasn't involved in in this work but

03:19:58.504 --> 03:20:00.980 I know it took a lot of hard work.

03:20:00.980 --> 03:20:02.495 Diligence are demonstrated.

03:20:02.495 --> 03:20:04.515 Essentially the same thing.

03:20:04.520 --> 03:20:05.892 The difference between these

03:20:05.892 --> 03:20:08.139 two mouse model is that this is

03:20:08.139 --> 03:20:09.832 a podocyte specific expression,

03:20:09.832 --> 03:20:12.976 whereas this is a back transgenic

03:20:12.976 --> 03:20:14.580 mice that if well,

03:20:14.580 --> 03:20:16.930 one expression is induced under

03:20:16.930 --> 03:20:18.964 the human promoter here.

03:20:18.964 --> 03:20:22.480 So this may probably mimic more of

03:20:22.480 --> 03:20:24.860 the Physiology that we see in humans,

03:20:24.860 --> 03:20:27.050 but the picture is the same

NOTE Confidence: 0.80177862625

03:20:27.050 --> 03:20:29.736 wherever there is the G1 and G2

NOTE Confidence: 0.80177862625

03:20:29.736 --> 03:20:31.268 you have high proteinuria.

NOTE Confidence: 0.80177862625

03:20:31.270 --> 03:20:32.332 And kidney disease.

NOTE Confidence: 0.80177862625

03:20:32.332 --> 03:20:34.102 So these studies establishes that

NOTE Confidence: 0.80177862625

03:20:34.102 --> 03:20:36.319 April 1 the risk are really well,

NOTE Confidence: 0.80177862625

03:20:36.320 --> 03:20:36.693 one.

NOTE Confidence: 0.80177862625

03:20:36.693 --> 03:20:38.931 They are not just risk factors

NOTE Confidence: 0.80177862625

03:20:38.931 --> 03:20:40.730 but drivers of disease,

NOTE Confidence: 0.80177862625

03:20:40.730 --> 03:20:43.446 working cell culture in my lab and

NOTE Confidence: 0.80177862625

03:20:43.446 --> 03:20:46.277 other groups then show further that the

NOTE Confidence: 0.80177862625

03:20:46.277 --> 03:20:49.146 degree of toxicity that you see with

NOTE Confidence: 0.80177862625

03:20:49.146 --> 03:20:52.466 this equal 1 depends on the expression level.

NOTE Confidence: 0.80177862625

03:20:52.470 --> 03:20:55.445 So it's not just a variant dependent

NOTE Confidence: 0.80177862625

03:20:55.445 --> 03:20:57.910 toxicity but also a dose effect.

NOTE Confidence: 0.80177862625

03:20:57.910 --> 03:20:59.722 So the more important one G1

316

NOTE Confidence: 0.80177862625

03:20:59.722 --> 03:21:00.930 and G2 you express,

NOTE Confidence: 0.80177862625

03:21:00.930 --> 03:21:03.200 the more toxicity you see.

NOTE Confidence: 0.80177862625

03:21:03.200 --> 03:21:05.216 The mechanism by which a poor one

NOTE Confidence: 0.80177862625

03:21:05.216 --> 03:21:07.238 causes injury is still under debate,

NOTE Confidence: 0.80177862625

03:21:07.240 --> 03:21:09.704 but a lot of the work that we've

NOTE Confidence: 0.80177862625

03:21:09.704 --> 03:21:11.653 done showing that one of the

NOTE Confidence: 0.80177862625

03:21:11.653 --> 03:21:14.067 proximal factor or effect is a loss

NOTE Confidence: 0.80177862625

03:21:14.067 --> 03:21:16.327 of intracellular potassium if one

NOTE Confidence: 0.80177862625

03:21:16.327 --> 03:21:18.516 itself might generalizes to the

NOTE Confidence: 0.80177862625

03:21:18.516 --> 03:21:20.396 membrane to the plasma membrane

NOTE Confidence: 0.80177862625

03:21:20.396 --> 03:21:22.640 and causes efflux of potassium.

NOTE Confidence: 0.80177862625

03:21:22.640 --> 03:21:26.198 Here I tried to summarize many

NOTE Confidence: 0.80177862625

03:21:26.200 --> 03:21:28.475 studies from many groups about

NOTE Confidence: 0.80177862625

03:21:28.475 --> 03:21:30.295 the effect of equipment,

NOTE Confidence: 0.80177862625

03:21:30.300 --> 03:21:33.168 kind of wrapping down the introduction.

NOTE Confidence: 0.859665591764706

03:21:33.170 --> 03:21:35.339 What does what is the effect of equal 1

NOTE Confidence: 0.859665591764706

03:21:35.339 --> 03:21:37.828 on the spectrum of diseases that we know?

NOTE Confidence: 0.859665591764706

03:21:37.830 --> 03:21:39.948 So these are diseases that have

NOTE Confidence: 0.859665591764706

03:21:39.948 --> 03:21:41.672 been associated with equal 1

NOTE Confidence: 0.859665591764706

03:21:41.672 --> 03:21:43.429 FSGS all the way down to lupus.

NOTE Confidence: 0.859665591764706

03:21:43.430 --> 03:21:45.662 So if you imagine that at the train

NOTE Confidence: 0.859665591764706

03:21:45.662 --> 03:21:47.697 station there are two groups of people.

NOTE Confidence: 0.859665591764706

03:21:47.700 --> 03:21:49.965 Groups that have normal variant

NOTE Confidence: 0.859665591764706

03:21:49.965 --> 03:21:52.934 did 0G0 and it group that carry

NOTE Confidence: 0.859665591764706

03:21:52.934 --> 03:21:55.680 higher risk of poelman. Genotype

NOTE Confidence: 0.87522534

03:21:58.150 --> 03:21:59.678 G1G1G2G2G1G2 those individuals at

NOTE Confidence: 0.87522534

03:21:59.678 --> 03:22:02.310 the train station are the ones that

NOTE Confidence: 0.87522534

03:22:02.310 --> 03:22:04.486 are more likely to get on the train.

NOTE Confidence: 0.87522534

03:22:04.490 --> 03:22:07.856 For example, if I see 10 black patient that

NOTE Confidence: 0.87522534

03:22:07.856 --> 03:22:11.047 have idiopathic FSGS in my in my clinic,

NOTE Confidence: 0.87522534

03:22:11.050 --> 03:22:13.948 7 out of of the 10 would have Iris

NOTE Confidence: 0.87522534

03:22:13.948 --> 03:22:16.782 Campbell and genotype that is quite

NOTE Confidence: 0.87522534

03:22:16.782 --> 03:22:18.004 outstanding, right? Remember,

NOTE Confidence: 0.87522534

03:22:18.004 --> 03:22:20.206 in the general for black population,

NOTE Confidence: 0.87522534

03:22:20.210 --> 03:22:22.863 only 10 to 15% of the black

NOTE Confidence: 0.87522534

03:22:22.863 --> 03:22:24.000 population carried this.

NOTE Confidence: 0.87522534

03:22:24.000 --> 03:22:28.515 There is genotype but among FSGS group.

NOTE Confidence: 0.87522534

03:22:28.520 --> 03:22:31.080 70% I do, and if you look down

NOTE Confidence: 0.87522534

03:22:31.080 --> 03:22:33.200 the list hypertension now,

NOTE Confidence: 0.87522534

03:22:33.200 --> 03:22:35.461 we found that COVID I will talk

NOTE Confidence: 0.87522534

03:22:35.461 --> 03:22:37.557 more about this in many cases

NOTE Confidence: 0.87522534

03:22:37.557 --> 03:22:39.317 in the largest group study,

NOTE Confidence: 0.87522534

03:22:39.320 --> 03:22:42.452 90% of people that develop COVID

NOTE Confidence: 0.87522534

03:22:42.452 --> 03:22:44.018 associated nephropathy karidis.

NOTE Confidence: 0.87522534

03:22:44.020 --> 03:22:47.110 So if well one genotype,

NOTE Confidence: 0.87522534

03:22:47.110 --> 03:22:50.780 hiris genotype increases the likelihood

NOTE Confidence: 0.87522534

03:22:50.780 --> 03:22:54.218 of developing this spectrum of disease.

NOTE Confidence: 0.87522534

03:22:54.220 --> 03:22:56.326 The second effect is that once

NOTE Confidence: 0.87522534

03:22:56.326 --> 03:22:58.609 the patient is on this train.

NOTE Confidence: 0.87522534

03:22:58.610 --> 03:23:00.710 Well, one is also an accelerant,

NOTE Confidence: 0.87522534

03:23:00.710 --> 03:23:03.536 it it it accelerate the progression

NOTE Confidence: 0.87522534

03:23:03.536 --> 03:23:04.949 to to dialysis.

NOTE Confidence: 0.87522534

03:23:04.950 --> 03:23:08.222 So if you ought to ESRD more specifically

NOTE Confidence: 0.87522534

03:23:08.222 --> 03:23:11.386 so this is a non equal 1 CKD train,

NOTE Confidence: 0.87522534

03:23:11.390 --> 03:23:13.702 this is the April 1 CKD train work

NOTE Confidence: 0.87522534

03:23:13.702 --> 03:23:15.715 from Ask Group and others shows

NOTE Confidence: 0.87522534

03:23:15.715 --> 03:23:18.156 that people that have a poor one

NOTE Confidence: 0.87522534

03:23:18.156 --> 03:23:20.361 in addition or in context of their

NOTE Confidence: 0.87522534

03:23:20.361 --> 03:23:22.194 CKD that their disease progressed

NOTE Confidence: 0.87522534

03:23:22.194 --> 03:23:24.582 to dialysis about 10 years on

NOTE Confidence: 0.87522534

03:23:24.582 --> 03:23:26.660 average earlier than regular CKD.

NOTE Confidence: 0.87522534

03:23:26.660 --> 03:23:28.310 And there's no known intervention.

NOTE Confidence: 0.87522534

03:23:28.310 --> 03:23:29.186 So far,

NOTE Confidence: 0.87522534

03:23:29.186 --> 03:23:32.690 so it's in this context that Kovid came

NOTE Confidence: 0.87522534

03:23:32.785 --> 03:23:36.978 and Kovid became essentially a perfect storm,

NOTE Confidence: 0.87522534

03:23:36.980 --> 03:23:39.325 because once COVID happened we

NOTE Confidence: 0.87522534

03:23:39.325 --> 03:23:41.201 it's quickly becoming apparent

NOTE Confidence: 0.87522534

03:23:41.201 --> 03:23:44.268 that some individuals who are

NOTE Confidence: 0.87522534

03:23:44.268 --> 03:23:46.158 developing collapsing glomerulopathy,

NOTE Confidence: 0.87522534

03:23:46.160 --> 03:23:48.509 but they I put this as a triangle here

NOTE Confidence: 0.87522534

03:23:48.509 --> 03:23:50.838 over 3 overlapping circle if you will.

NOTE Confidence: 0.87522534

03:23:50.840 --> 03:23:53.702 High risk equal 1 genotype covian

NOTE Confidence: 0.87522534

03:23:53.702 --> 03:23:56.512 infection and situations that cause people

NOTE Confidence: 0.87522534

03:23:56.512 --> 03:23:59.396 to develop COVID in the first place.

NOTE Confidence: 0.87522534

03:23:59.400 --> 03:24:02.574 The evidence that came from earlier

NOTE Confidence: 0.87522534

03:24:02.574 --> 03:24:05.307 studies from across the country

NOTE Confidence: 0.87522534

03:24:05.307 --> 03:24:08.457 shows that people that have COVID

NOTE Confidence: 0.87522534

03:24:08.460 --> 03:24:10.040 if you look at hospitalization,

NOTE Confidence: 0.87522534

03:24:10.040 --> 03:24:11.876 people inpatient hospitalization

NOTE Confidence: 0.87522534

03:24:11.876 --> 03:24:14.936 with complication with a Ki.

NOTE Confidence: 0.87522534

03:24:14.940 --> 03:24:16.910 Let me put it differently.

NOTE Confidence: 0.87522534

03:24:16.910 --> 03:24:19.086 I could clean jury,

NOTE Confidence: 0.87522534

03:24:19.086 --> 03:24:20.718 complicate COVID infection

NOTE Confidence: 0.87522534

03:24:20.718 --> 03:24:23.088 in about 46% of cases,

NOTE Confidence: 0.87522534

03:24:23.088 --> 03:24:26.070 meaning that almost half of patient but

NOTE Confidence: 0.87522534

03:24:26.153 --> 03:24:29.447 developed acute kidney injury from COVID.

NOTE Confidence: 0.87522534

03:24:29.450 --> 03:24:33.077 And if you look at patient in the ICU.

NOTE Confidence: 0.87522534

03:24:33.080 --> 03:24:34.950 Pretty much about three quarter

NOTE Confidence: 0.87522534

03:24:34.950 --> 03:24:36.446 of them developing care,

NOTE Confidence: 0.87522534

03:24:36.450 --> 03:24:38.625 and this actually has a

NOTE Confidence: 0.87522534

03:24:38.625 --> 03:24:40.365 significant effect on mortality.

NOTE Confidence: 0.87522534

03:24:40.370 --> 03:24:42.426 This is in this some of these early

NOTE Confidence: 0.87522534

03:24:42.426 --> 03:24:44.684 studies showing up to 50% mortality among

NOTE Confidence: 0.87522534

03:24:44.684 --> 03:24:49.003 patients with a Ki with kidney disease.

NOTE Confidence: 0.87522534

03:24:49.010 --> 03:24:51.586 Then they begin to biopsy this patient in

NOTE Confidence: 0.87522534

03:24:51.586 --> 03:24:54.449 the first aggregate study that was reported.

NOTE Confidence: 0.87522534

03:24:54.450 --> 03:24:56.963 This is an aggregate of 159

NOTE Confidence: 0.87522534

03:24:56.963 --> 03:24:59.128 patients from across the country.

NOTE Confidence: 0.87522534

03:24:59.130 --> 03:25:00.890 One of the four.

NOTE Confidence: 0.87522534

03:25:00.890 --> 03:25:03.090 Striking thing is the pathology.

NOTE Confidence: 0.87522534

03:25:03.090 --> 03:25:05.510 Shows that collapsing glomerulopathy

NOTE Confidence: 0.87522534

03:25:05.510 --> 03:25:08.535 is actually the most common

NOTE Confidence: 0.87522534

03:25:08.535 --> 03:25:10.138 histopathology in this API.

NOTE Confidence: 0.87522534

03:25:10.140 --> 03:25:12.284 In the first thirty.

NOTE Confidence: 0.87522534

03:25:12.284 --> 03:25:14.964 Then I kind of lab.

NOTE Confidence: 0.87522534

03:25:14.970 --> 03:25:17.354 In cancer is also did a study following

NOTE Confidence: 0.87522534

03:25:17.354 --> 03:25:20.008 up on this and to actually put the

NOTE Confidence: 0.87522534

03:25:20.008 --> 03:25:22.620 specific number on it anywhere between

NOTE Confidence: 0.87522534

03:25:22.620 --> 03:25:27.092 25 to 35% to 6% of histopathology

NOTE Confidence: 0.87522534

03:25:27.092 --> 03:25:30.524 from AK from COVID were covan.

NOTE Confidence: 0.87522534

03:25:30.524 --> 03:25:33.146 Now if you look before COVID,

NOTE Confidence: 0.755499288

03:25:33.150 --> 03:25:35.262 how many was a fraction of

NOTE Confidence: 0.755499288

03:25:35.262 --> 03:25:36.670 pathology that shows COVID?

NOTE Confidence: 0.755499288

03:25:36.670 --> 03:25:39.687 It's like 1.8 so this is a

NOTE Confidence: 0.755499288

03:25:39.687 --> 03:25:42.514 robust increase in in collapsing

NOTE Confidence: 0.755499288

03:25:42.514 --> 03:25:45.386 glomerulopathy from from COVID.

NOTE Confidence: 0.755499288

03:25:45.390 --> 03:25:47.588 And here is the here's the punch.

NOTE Confidence: 0.755499288

03:25:47.590 --> 03:25:50.656 If you look at this chain that

NOTE Confidence: 0.755499288

03:25:50.656 --> 03:25:51.970 had collapsing glomerulopathy

NOTE Confidence: 0.755499288

03:25:52.043 --> 03:25:54.158 from COVID and genotype them.

NOTE Confidence: 0.8297628375

03:25:56.440 --> 03:25:59.254 91.7% of them carry high risk genotype

NOTE Confidence: 0.8297628375

03:25:59.254 --> 03:26:02.833 compared to 10 to 15% of general population,

NOTE Confidence: 0.8297628375

03:26:02.833 --> 03:26:06.062 so this almost completes almost unity,

NOTE Confidence: 0.8297628375

03:26:06.062 --> 03:26:08.799 showing that having high risk Capital One

NOTE Confidence: 0.8297628375

03:26:08.799 --> 03:26:11.130 and developing collapsing glomerulopathy

NOTE Confidence: 0.8297628375

03:26:11.130 --> 03:26:13.840 from COVID almost one and the same.

NOTE Confidence: 0.8297628375

03:26:13.840 --> 03:26:16.332 In this setting these are images from

NOTE Confidence: 0.8297628375

03:26:16.332 --> 03:26:18.299 our recently published study showing

NOTE Confidence: 0.8297628375

03:26:18.299 --> 03:26:19.963 collapsing glomerulopathy where you

NOTE Confidence: 0.8297628375

03:26:19.963 --> 03:26:22.580 have the collapse of the glomerular.

NOTE Confidence: 0.8297628375

03:26:22.580 --> 03:26:25.429 Though you have injury of the usually.

NOTE Confidence: 0.8297628375

03:26:25.430 --> 03:26:28.664 Petrophile and hypoplasia of the put aside,

NOTE Confidence: 0.8297628375

03:26:28.670 --> 03:26:31.130 and ultimately resulting in podocyte

NOTE Confidence: 0.8297628375

03:26:31.130 --> 03:26:33.590 loss and loss of filtration.

NOTE Confidence: 0.8297628375

03:26:33.590 --> 03:26:36.050 The question came forward.

NOTE Confidence: 0.8297628375

03:26:36.050 --> 03:26:38.720 What is the mechanism by which

NOTE Confidence: 0.8297628375

03:26:38.720 --> 03:26:40.950 COVID causes a poor one?

NOTE Confidence: 0.8297628375

03:26:40.950 --> 03:26:42.646 Associate their collapsing glomerulopathy

NOTE Confidence: 0.8297628375

03:26:42.646 --> 03:26:44.766 so there were two theories.

NOTE Confidence: 0.8297628375

03:26:44.770 --> 03:26:47.416 One theory was that when I

03:26:47.416 --> 03:26:50.248 prothesis was that there's a direct

03:26:50.248 --> 03:26:52.688 viral infection of kidney cells.

03:26:52.690 --> 03:26:53.962 The evidence that supports

03:26:53.962 --> 03:26:55.552 this in part was that.

03:26:55.560 --> 03:26:58.200 And biopsy in autopsy study.

03:26:58.200 --> 03:27:00.490 There were reports initially that

03:27:00.490 --> 03:27:02.780 they were testicle that looked

03:27:02.852 --> 03:27:05.835 like viral vesical but in almost

03:27:05.835 --> 03:27:08.660 all biopsy from living patients,

03:27:08.660 --> 03:27:11.340 they're really not being compelling

03:27:11.340 --> 03:27:15.095 evidence that is direct viral infection of

03:27:15.095 --> 03:27:18.560 podocyte or or or kidney cell parenchyma,

03:27:18.560 --> 03:27:21.302 so that that sort of weakens

03:27:21.302 --> 03:27:22.673 the argument somewhat.

03:27:22.680 --> 03:27:25.116 Then there's the second equal thesis

NOTE Confidence: 0.8297628375

03:27:25.116 --> 03:27:27.140 that perhaps the cytokine storm

NOTE Confidence: 0.8297628375

03:27:27.140 --> 03:27:30.811 provoked by COVID triggered by COVID.

NOTE Confidence: 0.8297628375

03:27:30.811 --> 03:27:31.188 Actually,

NOTE Confidence: 0.8297628375

03:27:31.188 --> 03:27:34.210 homes on the kidney and causes glomerular.

NOTE Confidence: 0.8297628375

03:27:34.210 --> 03:27:36.484 Collapse either by April one through

NOTE Confidence: 0.8297628375

03:27:36.484 --> 03:27:39.411 April one or that means this hypothesis

NOTE Confidence: 0.8297628375

03:27:39.411 --> 03:27:41.646 is actually what we explored,

NOTE Confidence: 0.8297628375

03:27:41.650 --> 03:27:44.274 and the paper that came from it is

NOTE Confidence: 0.8297628375

03:27:44.274 --> 03:27:46.547 actually currently impressed in JCI insight,

NOTE Confidence: 0.8297628375

03:27:46.550 --> 03:27:48.926 so I encourage you to take a look and

NOTE Confidence: 0.8297628375

03:27:48.926 --> 03:27:51.559 it was led by the nephrology fellow

NOTE Confidence: 0.8297628375

03:27:51.559 --> 03:27:53.889 that Doctor Serene stream in the lab.

NOTE Confidence: 0.8297628375

03:27:53.890 --> 03:27:56.571 So what we did essentially was to

NOTE Confidence: 0.8297628375

03:27:56.571 --> 03:27:59.279 collaborate with our network pathologists.

NOTE Confidence: 0.8297628375

03:27:59.280 --> 03:28:02.436 Baby Thomas Astrid wine at Harvard

NOTE Confidence: 0.8297628375

03:28:02.436 --> 03:28:05.111 and David Thomas at Netherhall

NOTE Confidence: 0.8297628375

03:28:05.111 --> 03:28:07.949 and what we did was OK.

NOTE Confidence: 0.8297628375

03:28:07.950 --> 03:28:09.912 When you have patience that was

NOTE Confidence: 0.8297628375

03:28:09.912 --> 03:28:12.431 sent to you or biopsy that was

NOTE Confidence: 0.8297628375

03:28:12.431 --> 03:28:14.705 sent to you for collapsing FSGS,

NOTE Confidence: 0.8297628375

03:28:14.710 --> 03:28:17.806 let's genotype them so we have 9 cases.

NOTE Confidence: 0.8297628375

03:28:17.810 --> 03:28:19.858 What we found that of the nine cases

NOTE Confidence: 0.8297628375

03:28:19.858 --> 03:28:21.870 7 actually have high risk of where

NOTE Confidence: 0.8297628375

03:28:21.870 --> 03:28:24.498 one genotype. So that's 77 point.

NOTE Confidence: 0.8297628375

03:28:24.498 --> 03:28:26.034 You know 8%.

NOTE Confidence: 0.8297628375

03:28:26.040 --> 03:28:28.665 And even in this small sample set.

NOTE Confidence: 0.8297628375

03:28:28.670 --> 03:28:29.496 But interestingly.

NOTE Confidence: 0.8297628375

03:28:29.496 --> 03:28:30.322 Of course,

NOTE Confidence: 0.8297628375

03:28:30.322 --> 03:28:32.800 all of them were African Americans

NOTE Confidence: 0.8297628375

03:28:32.869 --> 03:28:35.172 except one person that is self described

NOTE Confidence: 0.8297628375

03:28:35.172 --> 03:28:37.897 as a white Hispanic and she has G1G1.

NOTE Confidence: 0.8297628375

03:28:37.897 --> 03:28:38.274 Also,

NOTE Confidence: 0.8297628375

03:28:38.274 --> 03:28:40.536 this betrays the point that I'm

NOTE Confidence: 0.8297628375

03:28:40.536 --> 03:28:42.398 saying before that the suspicion

NOTE Confidence: 0.8297628375

03:28:42.398 --> 03:28:45.278 should be there even for non

NOTE Confidence: 0.8297628375

03:28:45.278 --> 03:28:49.110 survey notified black individuals.

NOTE Confidence: 0.8297628375

03:28:49.110 --> 03:28:51.065 All of them have proteinuria

NOTE Confidence: 0.8297628375

03:28:51.065 --> 03:28:52.629 and progressive kidney disease,

NOTE Confidence: 0.8297628375

03:28:52.630 --> 03:28:54.190 and then we did immunity.

NOTE Confidence: 0.8297628375

03:28:54.190 --> 03:28:55.168 Immunohistochemistry for equal

NOTE Confidence: 0.8297628375

03:28:55.168 --> 03:28:57.450 1 to ask the question is equal

NOTE Confidence: 0.8297628375

03:28:57.507 --> 03:28:58.811 1 expression actually elevated

NOTE Confidence: 0.8297628375

03:28:58.811 --> 03:29:00.767 in the kidney of this patient.

NOTE Confidence: 0.8297628375

03:29:00.770 --> 03:29:03.830 So this is a biopsy reference.

NOTE Confidence: 0.8297628375

03:29:03.830 --> 03:29:06.196 No, no kidney disease in this patient.

NOTE Confidence: 0.8297628375

03:29:06.200 --> 03:29:07.289 There's no equal.

NOTE Confidence: 0.8297628375

03:29:07.289 --> 03:29:10.134 1 This was a patient with 0G0 who

NOTE Confidence: 0.8297628375

03:29:10.134 --> 03:29:12.126 had COVID but no kidney disease.

NOTE Confidence: 0.8297628375

03:29:12.130 --> 03:29:12.636 Again,

NOTE Confidence: 0.8297628375

03:29:12.636 --> 03:29:14.660 there's no equivalent expression,

NOTE Confidence: 0.8297628375

03:29:14.660 --> 03:29:17.180 but when we look at the kidney of

NOTE Confidence: 0.8297628375

03:29:17.180 --> 03:29:19.359 patients that had collapsed in FSGS.

NOTE Confidence: 0.8297628375

03:29:19.360 --> 03:29:21.586 This is a case of case six.

NOTE Confidence: 0.8297628375

03:29:21.590 --> 03:29:24.414 We saw robust expression in the portal site,

NOTE Confidence: 0.767181972857143

03:29:24.420 --> 03:29:27.864 but also in the glomerular endothelial cells,

NOTE Confidence: 0.767181972857143

03:29:27.870 --> 03:29:30.418 and this is uniform from across all

NOTE Confidence: 0.767181972857143

03:29:30.418 --> 03:29:32.619 the patients that we we examined.

NOTE Confidence: 0.767181972857143

03:29:32.620 --> 03:29:34.582 And this is just another view

NOTE Confidence: 0.767181972857143

03:29:34.582 --> 03:29:36.781 showing that we also saw staining

NOTE Confidence: 0.767181972857143

03:29:36.781 --> 03:29:38.836 in the period epithelial cells.

NOTE Confidence: 0.767181972857143

03:29:38.840 --> 03:29:41.682 But by and large it's podocyte and

NOTE Confidence: 0.767181972857143

03:29:41.682 --> 03:29:44.399 endothelial cells that had this expression.

NOTE Confidence: 0.767181972857143

03:29:44.400 --> 03:29:47.680 So what drives this expression of a poelman?

NOTE Confidence: 0.767181972857143

03:29:47.680 --> 03:29:49.610 Sarah looked at all the.

NOTE Confidence: 0.767181972857143

03:29:49.610 --> 03:29:52.660 Reported cytokines and chemokines that

NOTE Confidence: 0.767181972857143

03:29:52.660 --> 03:29:56.629 were reported to be elevated by COVID.

NOTE Confidence: 0.767181972857143

03:29:56.630 --> 03:29:58.550 And so we took each of them and

NOTE Confidence: 0.767181972857143

03:29:58.550 --> 03:30:00.706 sort of did a reductionist to see

NOTE Confidence: 0.767181972857143

03:30:00.706 --> 03:30:03.258 which one actually have an impact on

NOTE Confidence: 0.767181972857143

03:30:03.258 --> 03:30:05.026 increasingly poor one expression.

NOTE Confidence: 0.767181972857143

03:30:05.030 --> 03:30:06.770 As you can see here.

NOTE Confidence: 0.767181972857143

03:30:06.770 --> 03:30:09.808 I also I want better interferon alpha,

NOTE Confidence: 0.767181972857143

03:30:09.810 --> 03:30:11.835 beta gamma disturbing previously known

NOTE Confidence: 0.767181972857143

03:30:11.835 --> 03:30:15.149 to induce a poor one drive a poor

NOTE Confidence: 0.767181972857143

03:30:15.149 --> 03:30:17.174 one expression here for interferon

NOTE Confidence: 0.767181972857143

03:30:17.174 --> 03:30:19.112 gamma about 250 fold however.

NOTE Confidence: 0.767181972857143

03:30:19.112 --> 03:30:21.356 The interesting thing is when you

NOTE Confidence: 0.767181972857143

03:30:21.356 --> 03:30:23.884 have all the cytokines and you

NOTE Confidence: 0.767181972857143

03:30:23.884 --> 03:30:25.135 remove the interference,

NOTE Confidence: 0.767181972857143

03:30:25.140 --> 03:30:27.190 the known trigger you still

NOTE Confidence: 0.767181972857143

03:30:27.190 --> 03:30:29.240 have about 100 fold induction,

NOTE Confidence: 0.767181972857143

03:30:29.240 --> 03:30:31.620 meaning that even noninterference cytokines,

NOTE Confidence: 0.767181972857143

03:30:31.620 --> 03:30:32.640 especially in combination,

NOTE Confidence: 0.767181972857143

03:30:32.640 --> 03:30:35.020 have a robust effect on April 1

NOTE Confidence: 0.767181972857143

03:30:35.087 --> 03:30:37.025 expression and the second fact is

NOTE Confidence: 0.767181972857143

03:30:37.025 --> 03:30:39.105 that when you combine all these

NOTE Confidence: 0.767181972857143

03:30:39.105 --> 03:30:40.925 sycophants together that were released

NOTE Confidence: 0.767181972857143

03:30:40.925 --> 03:30:43.472 in context of COVID about more than

NOTE Confidence: 0.767181972857143

03:30:43.472 --> 03:30:46.060 6000 fold equal 1 expression was sent.

NOTE Confidence: 0.767181972857143

03:30:46.060 --> 03:30:48.258 This is an in glomerular endothelial cell.

NOTE Confidence: 0.767181972857143

03:30:48.260 --> 03:30:50.535 We saw the same pattern in primary.

NOTE Confidence: 0.767181972857143

03:30:50.540 --> 03:30:53.652 Photo site and then when we look at

NOTE Confidence: 0.767181972857143

03:30:53.652 --> 03:30:55.608 signaling pathway that potentially

NOTE Confidence: 0.767181972857143

03:30:55.608 --> 03:30:56.710 mediate this,

NOTE Confidence: 0.767181972857143

03:30:56.710 --> 03:30:59.338 the state 1/2 and three mediate

NOTE Confidence: 0.767181972857143

03:30:59.338 --> 03:31:02.490 the effect of the of the eight

NOTE Confidence: 0.767181972857143

03:31:02.490 --> 03:31:04.670 key cytokines that we see,

NOTE Confidence: 0.767181972857143

03:31:04.670 --> 03:31:07.050 and we use various city name which

NOTE Confidence: 0.767181972857143

03:31:07.050 --> 03:31:09.416 is an inhibitor of the Jack one

NOTE Confidence: 0.767181972857143

03:31:09.416 --> 03:31:11.796 Jack two which are necessary to to

NOTE Confidence: 0.767181972857143

03:31:11.796 --> 03:31:13.642 activate these three stacks and

NOTE Confidence: 0.767181972857143

03:31:13.642 --> 03:31:15.994 you can see both in the glomerular

NOTE Confidence: 0.767181972857143

03:31:15.994 --> 03:31:17.509 endothelial cells and podocyte.

NOTE Confidence: 0.767181972857143

03:31:17.510 --> 03:31:19.440 It totally abrogate the expression

NOTE Confidence: 0.767181972857143

03:31:19.440 --> 03:31:21.770 of equal 1 so suggesting that.

NOTE Confidence: 0.767181972857143

03:31:21.770 --> 03:31:24.470 This site outlines converges through the

NOTE Confidence: 0.767181972857143

03:31:24.470 --> 03:31:28.118 same Jack stat pathway to induce a power.

NOTE Confidence: 0.767181972857143

03:31:28.118 --> 03:31:29.966 One expression summarized here.

NOTE Confidence: 0.767181972857143

03:31:29.970 --> 03:31:33.870 So again, cytokine storm from COVID.

NOTE Confidence: 0.767181972857143

03:31:33.870 --> 03:31:35.018 Interacting with their ligand

NOTE Confidence: 0.767181972857143

03:31:35.018 --> 03:31:37.108 in photo site and in the philia

NOTE Confidence: 0.767181972857143

03:31:37.108 --> 03:31:39.299 cell and driving it well when the

NOTE Confidence: 0.767181972857143

03:31:39.299 --> 03:31:40.889 expression through a common pathway.

NOTE Confidence: 0.767181972857143

03:31:40.890 --> 03:31:41.181 Here,

NOTE Confidence: 0.767181972857143

03:31:41.181 --> 03:31:42.927 showing that that one and that

NOTE Confidence: 0.767181972857143

03:31:42.927 --> 03:31:44.410 Barry sitting it blocks it.

NOTE Confidence: 0.767181972857143

03:31:44.410 --> 03:31:46.390 So to drive this home further.

NOTE Confidence: 0.767181972857143

03:31:46.390 --> 03:31:51.348 So what if we get I PST we we make I

NOTE Confidence: 0.767181972857143

03:31:51.350 --> 03:31:54.068 PSC's from individual that has G1G2,

NOTE Confidence: 0.767181972857143

03:31:54.068 --> 03:31:55.958 and then we differentiated those

NOTE Confidence: 0.767181972857143

03:31:55.958 --> 03:31:57.470 using the standard protocol.

NOTE Confidence: 0.767181972857143

03:31:57.470 --> 03:31:59.305 This was from Melissa Little

NOTE Confidence: 0.767181972857143

03:31:59.305 --> 03:32:01.589 Protocol to make micro kidney micro

NOTE Confidence: 0.767181972857143

03:32:01.589 --> 03:32:03.869 organoid that had what they produce.

NOTE Confidence: 0.767181972857143

03:32:03.870 --> 03:32:05.796 Like a lot of endothelial cells,

NOTE Confidence: 0.767181972857143

03:32:05.800 --> 03:32:08.680 but a lot of producers that Chevrolet cells.

NOTE Confidence: 0.767181972857143

03:32:08.680 --> 03:32:10.984 And then what we did was to treat

NOTE Confidence: 0.767181972857143

03:32:10.984 --> 03:32:13.178 them or not with interference.

NOTE Confidence: 0.767181972857143

03:32:13.180 --> 03:32:15.058 So in the absence of interference,

NOTE Confidence: 0.767181972857143

03:32:15.060 --> 03:32:17.210 there's really not much equipment

NOTE Confidence: 0.767181972857143

03:32:17.210 --> 03:32:18.380 expression with interference.

NOTE Confidence: 0.767181972857143

03:32:18.380 --> 03:32:20.600 You see robust equal 1 induction,

NOTE Confidence: 0.767181972857143

03:32:20.600 --> 03:32:23.888 especially in the part that are

NOTE Confidence: 0.767181972857143

03:32:23.888 --> 03:32:25.532 positive for podocalyxin.

NOTE Confidence: 0.767181972857143

03:32:25.540 --> 03:32:25.918 Again,

NOTE Confidence: 0.767181972857143

03:32:25.918 --> 03:32:27.808 the part that is consistent

NOTE Confidence: 0.767181972857143

03:32:27.808 --> 03:32:30.199 with podocyte when we applied by

NOTE Confidence: 0.767181972857143

03:32:30.199 --> 03:32:31.819 reciting name the blocks,

NOTE Confidence: 0.767181972857143

03:32:31.820 --> 03:32:33.288 the expression when we

NOTE Confidence: 0.767181972857143

03:32:33.288 --> 03:32:34.756 applied all the cytokines.

NOTE Confidence: 0.767181972857143

03:32:34.760 --> 03:32:36.638 That I should before it gained

NOTE Confidence: 0.767181972857143

03:32:36.638 --> 03:32:38.652 robust induction and the effect of

NOTE Confidence: 0.767181972857143

03:32:38.652 --> 03:32:40.392 all those cytokines were similarly

NOTE Confidence: 0.767181972857143

03:32:40.392 --> 03:32:41.436 blocked by Barry

NOTE Confidence: 0.695061666173913

03:32:41.494 --> 03:32:42.748 sitting in consistent.

NOTE Confidence: 0.695061666173913

03:32:42.750 --> 03:32:45.228 That even in this patient derived

NOTE Confidence: 0.695061666173913

03:32:45.230 --> 03:32:47.685 kidney organoid that these cytokines

NOTE Confidence: 0.695061666173913

03:32:47.685 --> 03:32:50.770 work through the Jack stat pathway

NOTE Confidence: 0.695061666173913

03:32:50.770 --> 03:32:52.805 functionally do do this have

NOTE Confidence: 0.695061666173913

03:32:52.805 --> 03:32:55.550 functional effect in terms of toxicity.

NOTE Confidence: 0.695061666173913

03:32:55.550 --> 03:32:57.530 We confirm the equivalent expression

NOTE Confidence: 0.695061666173913

03:32:57.530 --> 03:33:00.741 here at 96 hours and we look at

NOTE Confidence: 0.695061666173913

03:33:00.741 --> 03:33:02.289 viability so viability wise,

NOTE Confidence: 0.695061666173913

03:33:02.290 --> 03:33:05.418 as you had interferon or all the cytokines.

NOTE Confidence: 0.695061666173913

03:33:05.420 --> 03:33:07.793 You see a reduction in the viability

03:33:07.793 --> 03:33:10.677 when you add baricitinib it rescued it.

03:33:10.680 --> 03:33:12.976 We look at ATP as just another

03:33:12.976 --> 03:33:15.319 measure of cell that is viability.

03:33:15.320 --> 03:33:17.702 So this data suggests that the

03:33:17.702 --> 03:33:20.174 expression of equal 1 at least

03:33:20.174 --> 03:33:22.598 downstream of the Jack stat pathway

03:33:22.598 --> 03:33:26.107 might be a mediator of what we see with

03:33:26.107 --> 03:33:28.338 collapsing FSGS as shown in this model.

03:33:28.338 --> 03:33:30.782 So I went over that kind of quickly

03:33:30.782 --> 03:33:32.567 because the the manuscript is

03:33:32.567 --> 03:33:34.660 now submitted and and and it's

03:33:34.660 --> 03:33:35.928 online and JCI insight.

03:33:35.930 --> 03:33:39.098 Encourage us to look at it.

03:33:39.100 --> 03:33:40.665 How do we translate this

03:33:40.665 --> 03:33:41.917 now by reciting name?

03:33:41.920 --> 03:33:44.164 Actually I believe yesterday or two

NOTE Confidence: 0.695061666173913

03:33:44.164 --> 03:33:47.034 days ago received a full FDA approval

NOTE Confidence: 0.695061666173913

03:33:47.034 --> 03:33:49.209 for treatment of COVID infection

NOTE Confidence: 0.695061666173913

03:33:49.209 --> 03:33:51.807 that requires that oxygenation in the

NOTE Confidence: 0.695061666173913

03:33:51.807 --> 03:33:54.291 hospital it's not approved for COVAN,

NOTE Confidence: 0.695061666173913

03:33:54.300 --> 03:33:56.540 which is a complication,

NOTE Confidence: 0.695061666173913

03:33:56.540 --> 03:33:59.152 but this study suggests a couple of

NOTE Confidence: 0.695061666173913

03:33:59.152 --> 03:34:01.940 things that the use of various citizens,

NOTE Confidence: 0.695061666173913

03:34:01.940 --> 03:34:04.130 at least for treatment of COVID

NOTE Confidence: 0.695061666173913

03:34:04.130 --> 03:34:05.996 should be explored as people

NOTE Confidence: 0.695061666173913

03:34:05.996 --> 03:34:08.692 were using this now is is now FDA

NOTE Confidence: 0.695061666173913

03:34:08.692 --> 03:34:10.479 approved for COVID in itself.

NOTE Confidence: 0.695061666173913

03:34:10.480 --> 03:34:12.784 The role of equal 1 genotyping

NOTE Confidence: 0.695061666173913

03:34:12.784 --> 03:34:14.760 I think is underscored here,

NOTE Confidence: 0.695061666173913

03:34:14.760 --> 03:34:16.734 especially in the context of people that

NOTE Confidence: 0.695061666173913

03:34:16.734 --> 03:34:19.099 have a poor one related kidney disease.

NOTE Confidence: 0.695061666173913

03:34:19.100 --> 03:34:21.420 I put a question mark on the trial.

NOTE Confidence: 0.695061666173913

03:34:21.420 --> 03:34:23.800 This would be the study the use

NOTE Confidence: 0.695061666173913

03:34:23.800 --> 03:34:25.708 of various citizen for treating

NOTE Confidence: 0.695061666173913

03:34:25.708 --> 03:34:28.156 disease need to be tested properly.

NOTE Confidence: 0.695061666173913

03:34:28.160 --> 03:34:31.055 There was suggestion initially that

NOTE Confidence: 0.695061666173913

03:34:31.055 --> 03:34:33.371 perhaps exogenous interference could

NOTE Confidence: 0.695061666173913

03:34:33.371 --> 03:34:37.085 be used as part of treatment for

NOTE Confidence: 0.695061666173913

03:34:37.085 --> 03:34:39.121 COVID because interferon deficiency.

NOTE Confidence: 0.695061666173913

03:34:39.130 --> 03:34:42.370 Seems to increase the risk of.

NOTE Confidence: 0.695061666173913

03:34:42.370 --> 03:34:45.160 Contracting kovid and having severe COVID.

NOTE Confidence: 0.695061666173913

03:34:45.160 --> 03:34:47.512 Our study here suggests that maybe for

NOTE Confidence: 0.695061666173913

03:34:47.512 --> 03:34:50.138 patient that at risk I have high risk of,

NOTE Confidence: 0.695061666173913

03:34:50.140 --> 03:34:51.920 well, one genotype given them,

NOTE Confidence: 0.695061666173913

03:34:51.920 --> 03:34:54.570 interferon could actually be heading

NOTE Confidence: 0.695061666173913

03:34:54.570 --> 03:34:58.139 flame or hiding gasoline to the flame,

NOTE Confidence: 0.695061666173913

03:34:58.140 --> 03:35:01.000 and probably should be avoided.

NOTE Confidence: 0.695061666173913

03:35:01.000 --> 03:35:04.017 Our transition quickly to the second story,

NOTE Confidence: 0.695061666173913

03:35:04.020 --> 03:35:06.610 but this one I not much time.

NOTE Confidence: 0.695061666173913

03:35:06.610 --> 03:35:08.920 Not everyone at the train station

NOTE Confidence: 0.695061666173913

03:35:08.920 --> 03:35:10.075 developed kidney disease.

NOTE Confidence: 0.695061666173913

03:35:10.080 --> 03:35:11.616 Not everyone get on the train.

NOTE Confidence: 0.695061666173913

03:35:11.620 --> 03:35:13.012 That's going to dialysis.

NOTE Confidence: 0.695061666173913

03:35:13.012 --> 03:35:15.963 So one of the question of interest in

NOTE Confidence: 0.695061666173913

03:35:15.963 --> 03:35:18.339 my lab is what differentiates people

NOTE Confidence: 0.695061666173913

03:35:18.339 --> 03:35:20.767 that have the high risk genotype.

NOTE Confidence: 0.695061666173913

03:35:20.770 --> 03:35:22.492 And people who have the high risk

NOTE Confidence: 0.695061666173913

03:35:22.492 --> 03:35:23.970 genotype and develop kidney disease.

NOTE Confidence: 0.695061666173913

03:35:23.970 --> 03:35:26.448 We think there's a three hit necessary.

NOTE Confidence: 0.695061666173913

03:35:26.450 --> 03:35:28.580 First hit mainly high risk equals

NOTE Confidence: 0.695061666173913

03:35:28.580 --> 03:35:29.992 one genotype. Second hidden.

NOTE Confidence: 0.695061666173913

03:35:29.992 --> 03:35:32.098 In this case we use interferon

340

NOTE Confidence: 0.695061666173913

03:35:32.098 --> 03:35:34.399 but other cytokines as our COVID

NOTE Confidence: 0.695061666173913

03:35:34.399 --> 03:35:35.548 studies have shown.

NOTE Confidence: 0.695061666173913

03:35:35.550 --> 03:35:38.630 But even when these two hits are present,

NOTE Confidence: 0.695061666173913

03:35:38.630 --> 03:35:41.414 we know from HIV that not all those

NOTE Confidence: 0.695061666173913

03:35:41.414 --> 03:35:43.229 people develop kidney disease.

NOTE Confidence: 0.695061666173913

03:35:43.230 --> 03:35:45.510 Only 20% of them do.

NOTE Confidence: 0.695061666173913

03:35:45.510 --> 03:35:47.466 Then there must be some intrinsic

NOTE Confidence: 0.695061666173913

03:35:47.466 --> 03:35:49.566 factor that is unique to the

NOTE Confidence: 0.695061666173913

03:35:49.566 --> 03:35:51.030 patients that develop disease.

NOTE Confidence: 0.695061666173913

03:35:51.030 --> 03:35:52.530 That could be teased out,

NOTE Confidence: 0.695061666173913

03:35:52.530 --> 03:35:56.962 so we took a I PSC's approach

NOTE Confidence: 0.695061666173913

03:35:56.962 --> 03:35:58.636 to to circulate.

NOTE Confidence: 0.640947831111111

03:35:58.640 --> 03:35:59.976 We identify patient with

NOTE Confidence: 0.640947831111111

03:35:59.976 --> 03:36:01.646 FSGS that have virus deep.

NOTE Confidence: 0.640947831111111

03:36:01.650 --> 03:36:03.105 Well one genotype.

NOTE Confidence: 0.640947831111111

03:36:03.105 --> 03:36:05.045 We identify healthy controls.

NOTE Confidence: 0.640947831111111

03:36:05.050 --> 03:36:06.890 We make IPS from them.

NOTE Confidence: 0.640947831111111

03:36:06.890 --> 03:36:09.098 We differentiate these two photo sites

NOTE Confidence: 0.640947831111111

03:36:09.098 --> 03:36:10.999 and then we perform transcriptomic

NOTE Confidence: 0.640947831111111

03:36:10.999 --> 03:36:13.533 analysis to sort of try and glean

NOTE Confidence: 0.640947831111111

03:36:13.533 --> 03:36:16.145 out what could be the effect of this

NOTE Confidence: 0.640947831111111

03:36:16.145 --> 03:36:18.492 modifier and how can we understand it.

NOTE Confidence: 0.640947831111111

03:36:18.492 --> 03:36:21.110 What we did in a nutshell here.

NOTE Confidence: 0.640947831111111

03:36:21.110 --> 03:36:22.905 Was to compare high risk

NOTE Confidence: 0.640947831111111

03:36:22.905 --> 03:36:24.700 cases and high risk control.

NOTE Confidence: 0.640947831111111

03:36:24.700 --> 03:36:26.919 These were limited number of of controls

NOTE Confidence: 0.640947831111111

03:36:26.919 --> 03:36:28.979 and we did a transcriptomic analysis

NOTE Confidence: 0.640947831111111

03:36:28.979 --> 03:36:31.872 to see what are the genes that are

NOTE Confidence: 0.640947831111111

03:36:31.872 --> 03:36:33.436 differentially more upregulated in

NOTE Confidence: 0.640947831111111

03:36:33.436 --> 03:36:35.831 the high risk cases than control.

NOTE Confidence: 0.640947831111111

03:36:35.831 --> 03:36:38.848 And many of those genes are downstream

NOTE Confidence: 0.640947831111111

03:36:38.848 --> 03:36:41.479 again of the Jack stat pathway,

NOTE Confidence: 0.640947831111111

03:36:41.480 --> 03:36:44.426 suggesting that the Jack stat pathway

NOTE Confidence: 0.640947831111111

03:36:44.426 --> 03:36:47.200 is more potentiated in the podocyte of

NOTE Confidence: 0.640947831111111

03:36:47.200 --> 03:36:50.040 people who are at risk of developing.

NOTE Confidence: 0.640947831111111

03:36:50.040 --> 03:36:51.600 If well, one related.

NOTE Confidence: 0.640947831111111

03:36:51.600 --> 03:36:54.452 FSGS we went further to actually validate

NOTE Confidence: 0.640947831111111

03:36:54.452 --> 03:36:57.490 this to see when we applied interferon.

NOTE Confidence: 0.640947831111111

03:36:57.490 --> 03:37:00.710 What is the equal 1 expression level

NOTE Confidence: 0.640947831111111

03:37:00.710 --> 03:37:02.852 in podocyte from cases than control

NOTE Confidence: 0.640947831111111

03:37:02.852 --> 03:37:05.229 we saw more equal 1 expression.

NOTE Confidence: 0.640947831111111

03:37:05.230 --> 03:37:07.612 We saw more upregulation of the

NOTE Confidence: 0.640947831111111

03:37:07.612 --> 03:37:10.510 Jack stat pathway and all this can

NOTE Confidence: 0.640947831111111

03:37:10.510 --> 03:37:12.570 be blocked actually by various.

NOTE Confidence: 0.640947831111111

03:37:12.570 --> 03:37:14.988 We confirm this by Western blot

NOTE Confidence: 0.640947831111111

03:37:14.990 --> 03:37:17.010 and downstream of April 1.

NOTE Confidence: 0.640947831111111

03:37:17.010 --> 03:37:18.630 Given the work in my lab,

NOTE Confidence: 0.640947831111111

03:37:18.630 --> 03:37:20.892 we know that April 1 mediate

NOTE Confidence: 0.640947831111111

03:37:20.892 --> 03:37:21.646 potassium efflux,

NOTE Confidence: 0.640947831111111

03:37:21.650 --> 03:37:23.687 so we did use a potassium tracer,

NOTE Confidence: 0.640947831111111

03:37:23.690 --> 03:37:25.550 which is rubidium to see what

NOTE Confidence: 0.640947831111111

03:37:25.550 --> 03:37:27.851 happened in a case when we induce

NOTE Confidence: 0.640947831111111

03:37:27.851 --> 03:37:30.161 the puelo one with interferon to the

NOTE Confidence: 0.640947831111111

03:37:30.225 --> 03:37:32.487 rubidium with loaded into the cell,

NOTE Confidence: 0.640947831111111

03:37:32.490 --> 03:37:35.166 you see significant reduction in rubidium,

NOTE Confidence: 0.640947831111111

03:37:35.170 --> 03:37:37.620 and there are some rescue with Barry

NOTE Confidence: 0.640947831111111

03:37:37.620 --> 03:37:39.399 sitting them against showing that

NOTE Confidence: 0.640947831111111

03:37:39.399 --> 03:37:41.737 even in these I PSC photosite model.

NOTE Confidence: 0.640947831111111

03:37:41.740 --> 03:37:44.620 It's recapitulating what we see.

NOTE Confidence: 0.640947831111111

03:37:44.620 --> 03:37:46.240 We did a knockout of April,

NOTE Confidence: 0.640947831111111

03:37:46.240 --> 03:37:47.740 one in one of the line,

NOTE Confidence: 0.640947831111111

03:37:47.740 --> 03:37:50.758 and the potassium efflux was abrogated.

NOTE Confidence: 0.640947831111111

03:37:50.760 --> 03:37:53.415 So this led us to to to to to

NOTE Confidence: 0.640947831111111

03:37:53.415 --> 03:37:55.320 write a proposal to say,

NOTE Confidence: 0.640947831111111

03:37:55.320 --> 03:37:57.636 well maybe we should try baricitinib

NOTE Confidence: 0.640947831111111

03:37:57.636 --> 03:38:00.039 as a potential therapy for it well,

NOTE Confidence: 0.640947831111111

03:38:00.040 --> 03:38:03.260 but having the drug and the treatment

NOTE Confidence: 0.640947831111111

03:38:03.260 --> 03:38:05.735 is one thing helping people who

NOTE Confidence: 0.640947831111111

03:38:05.735 --> 03:38:07.560 actually need those drug and

NOTE Confidence: 0.640947831111111

03:38:07.560 --> 03:38:09.568 treatment to accept it to use it.

NOTE Confidence: 0.640947831111111

03:38:09.570 --> 03:38:10.851 It's another entirely.

NOTE Confidence: 0.640947831111111

03:38:10.851 --> 03:38:12.559 There's a lack of.

NOTE Confidence: 0.640947831111111

03:38:12.560 --> 03:38:14.532 Awareness about kidney disease

NOTE Confidence: 0.640947831111111

03:38:14.532 --> 03:38:16.504 in the black community.

NOTE Confidence: 0.640947831111111

03:38:16.510 --> 03:38:18.000 This lack of specific people,

NOTE Confidence: 0.640947831111111

03:38:18.000 --> 03:38:19.275 one treatment which is part

NOTE Confidence: 0.640947831111111

03:38:19.275 --> 03:38:20.550 of what we're working on.

NOTE Confidence: 0.640947831111111

03:38:20.550 --> 03:38:23.043 And if you look at clinical trials as well,

NOTE Confidence: 0.640947831111111

03:38:23.050 --> 03:38:25.690 one of kidney disease in general,

NOTE Confidence: 0.640947831111111

03:38:25.690 --> 03:38:28.190 black represent less than 5%.

NOTE Confidence: 0.640947831111111

03:38:28.190 --> 03:38:30.774 So to really translate some of this work,

NOTE Confidence: 0.640947831111111

03:38:30.780 --> 03:38:33.209 we really need to address this issue,

NOTE Confidence: 0.640947831111111

03:38:33.210 --> 03:38:36.720 and that's what led us to the the study

NOTE Confidence: 0.640947831111111

03:38:36.720 --> 03:38:41.910 that we we is now funded by Nida by NIMH D.

NOTE Confidence: 0.640947831111111

03:38:41.910 --> 03:38:42.920 We call it the care.

NOTE Confidence: 0.640947831111111

03:38:42.920 --> 03:38:44.138 And justice study.

NOTE Confidence: 0.640947831111111

03:38:44.138 --> 03:38:46.168 The study has three aims.

NOTE Confidence: 0.640947831111111

03:38:46.170 --> 03:38:48.450 The aim first aim is community

NOTE Confidence: 0.640947831111111

03:38:48.450 --> 03:38:50.469 engagement and and registry and

NOTE Confidence: 0.640947831111111

03:38:50.469 --> 03:38:52.197 screening for kidney disease.

NOTE Confidence: 0.640947831111111

03:38:52.200 --> 03:38:54.584 So here we screen people for kidney disease.

NOTE Confidence: 0.640947831111111

03:38:54.590 --> 03:38:56.750 We screen them we we genotype

NOTE Confidence: 0.640947831111111

03:38:56.750 --> 03:38:59.439 them and people who are eligible

NOTE Confidence: 0.640947831111111

03:38:59.439 --> 03:39:01.787 who have clinically significant

NOTE Confidence: 0.640947831111111

03:39:01.787 --> 03:39:03.792 proteinuria and kidney disease will

NOTE Confidence: 0.640947831111111

03:39:03.792 --> 03:39:05.910 be eligible to participate in justice,

NOTE Confidence: 0.640947831111111

03:39:05.910 --> 03:39:07.176 trial and justice.

NOTE Confidence: 0.640947831111111

03:39:07.176 --> 03:39:08.864 Essentially stand for Janus

NOTE Confidence: 0.640947831111111

03:39:08.864 --> 03:39:10.130 kinase that inhibition

NOTE Confidence: 0.658159801428571

03:39:10.130 --> 03:39:12.937 to reduce equal 1 associated kidney disease.

NOTE Confidence: 0.658159801428571

03:39:12.940 --> 03:39:15.874 So we kind of pursuing care to do justice.

NOTE Confidence: 0.658159801428571

03:39:15.880 --> 03:39:17.560 The third part is to actually

NOTE Confidence: 0.658159801428571

03:39:17.560 --> 03:39:19.060 do justice in a dish.

NOTE Confidence: 0.658159801428571

03:39:19.060 --> 03:39:20.996 I will not talk much about this here,

NOTE Confidence: 0.658159801428571

03:39:21.000 --> 03:39:22.470 and we've sort of with a

NOTE Confidence: 0.658159801428571

03:39:22.470 --> 03:39:23.940 lot of work and effort.

NOTE Confidence: 0.658159801428571

03:39:23.940 --> 03:39:25.500 I encourage you to check out

NOTE Confidence: 0.658159801428571

03:39:25.500 --> 03:39:27.070 this study website as well. It's

NOTE Confidence: 0.910948620909091

03:39:30.140 --> 03:39:30.555 www.kidneycareandjustice.com.

NOTE Confidence: 0.910948620909091

03:39:30.555 --> 03:39:33.460 The goal here is to engage the

NOTE Confidence: 0.910948620909091

03:39:33.460 --> 03:39:34.890 African American community.

NOTE Confidence: 0.910948620909091

03:39:34.890 --> 03:39:37.354 We are starting small here in North Carolina,

NOTE Confidence: 0.910948620909091

03:39:37.360 --> 03:39:38.600 but we're getting a lot

NOTE Confidence: 0.910948620909091

03:39:38.600 --> 03:39:39.592 of interest from outside,

NOTE Confidence: 0.910948620909091

03:39:39.600 --> 03:39:41.502 but we have to find resources

NOTE Confidence: 0.910948620909091

03:39:41.502 --> 03:39:43.310 to actually expand this further.

NOTE Confidence: 0.910948620909091

03:39:43.310 --> 03:39:46.705 To provide free screening for kidney disease.

NOTE Confidence: 0.910948620909091

03:39:46.710 --> 03:39:49.216 To provide free equal 1 genotyping research

NOTE Confidence: 0.910948620909091

03:39:49.216 --> 03:39:51.868 based and for people who are eligible,

NOTE Confidence: 0.910948620909091

03:39:51.870 --> 03:39:55.100 especially people with FSGS or

NOTE Confidence: 0.910948620909091

03:39:55.100 --> 03:39:56.106 hypertensive nephrosclerosis,

NOTE Confidence: 0.910948620909091

03:39:56.106 --> 03:39:58.242 they will be eligible to enroll

NOTE Confidence: 0.910948620909091

03:39:58.242 --> 03:40:00.688 in a six month clinical trial,

NOTE Confidence: 0.910948620909091

03:40:00.690 --> 03:40:02.850 baricitinib of which primary end

NOTE Confidence: 0.910948620909091

03:40:02.850 --> 03:40:05.010 point is reduction of proteinuria.

NOTE Confidence: 0.910948620909091

03:40:05.010 --> 03:40:07.290 So because in the interest of

NOTE Confidence: 0.910948620909091

03:40:07.290 --> 03:40:09.270 time I'll I'll pause here,

NOTE Confidence: 0.910948620909091

03:40:09.270 --> 03:40:11.446 I know I've gone through this a little

NOTE Confidence: 0.910948620909091

03:40:11.446 --> 03:40:13.486 quickly to to engage question and to.

NOTE Confidence: 0.910948620909091

03:40:13.490 --> 03:40:16.736 Leave room for some back and forth again.

NOTE Confidence: 0.910948620909091

03:40:16.736 --> 03:40:19.584 I want to thank people in my lab.

NOTE Confidence: 0.910948620909091

03:40:19.590 --> 03:40:21.765 Who basically have done all

NOTE Confidence: 0.910948620909091

03:40:21.765 --> 03:40:23.505 the work my collaborator,

NOTE Confidence: 0.910948620909091

03:40:23.510 --> 03:40:26.426 especially on the COVID covan project

NOTE Confidence: 0.910948620909091

03:40:26.426 --> 03:40:28.370 at Doctor Thomas Neuropathologist.

NOTE Confidence: 0.910948620909091

03:40:28.370 --> 03:40:30.209 Doctor Wayne Nephro,

NOTE Confidence: 0.910948620909091

03:40:30.209 --> 03:40:32.048 pathologist at Harvard,

NOTE Confidence: 0.910948620909091

03:40:32.050 --> 03:40:33.886 and our funding agencies,

NOTE Confidence: 0.910948620909091

03:40:33.886 --> 03:40:38.109 so I'll pause here to to take questions.

NOTE Confidence: 0.910948620909091

03:40:38.110 --> 03:40:38.680 Thank you.

NOTE Confidence: 0.864947603333333

03:40:48.980 --> 03:40:49.748 That was great.

NOTE Confidence: 0.6203507

03:40:52.350 --> 03:40:54.930 Doctor garashi so thank

NOTE Confidence: 0.6203507

03:40:54.930 --> 03:40:56.105 you for that great talk.

NOTE Confidence: 0.43108156

03:41:04.470 --> 03:41:04.810 These

NOTE Confidence: 0.607870775

03:41:14.490 --> 03:41:19.128 are these are organoids purified podocytes.

NOTE Confidence: 0.607870775

03:41:19.130 --> 03:41:23.156 Or are they just standard organoids?

NOTE Confidence: 0.607870775

03:41:23.160 --> 03:41:27.020 So for the COVID project these

NOTE Confidence: 0.607870775

03:41:27.020 --> 03:41:30.300 are derived micro organoids,

NOTE Confidence: 0.607870775

03:41:30.300 --> 03:41:32.120 so they were differentiated,

NOTE Confidence: 0.607870775

03:41:32.120 --> 03:41:34.395 so these were not isolated

NOTE Confidence: 0.607870775

03:41:34.395 --> 03:41:36.220 from patients kidneys.

NOTE Confidence: 0.607870775

03:41:36.220 --> 03:41:38.620 What we did was essentially to

NOTE Confidence: 0.607870775

03:41:38.620 --> 03:41:41.020 take the blood from patients.

NOTE Confidence: 0.607870775

03:41:41.020 --> 03:41:44.300 We isolate peripheral blood monocytes

NOTE Confidence: 0.607870775

03:41:44.300 --> 03:41:46.315 and then we transduce peripheral

03:41:46.315 --> 03:41:48.875 blood monocyte with the four Yamanaka

03:41:48.875 --> 03:41:51.695 factors to reprogram them to become

03:41:51.695 --> 03:41:53.570 inducible pluripotent stem cells.

03:41:53.570 --> 03:41:55.964 One is it become pluripotent stem cells,

03:41:55.970 --> 03:41:57.558 then we differentiate them

03:41:57.558 --> 03:41:58.749 using established protocol.

03:41:58.750 --> 03:42:00.086 A lot of folks,

03:42:00.086 --> 03:42:02.590 both at Harvard and and and Melissa

03:42:02.590 --> 03:42:05.523 Little at the entry and Melissa Little

03:42:05.523 --> 03:42:08.390 Lab did the pioneering work here.

03:42:08.390 --> 03:42:11.029 So the protocol is actually now standard,

03:42:11.030 --> 03:42:13.958 where you can coax this IPSC to become

03:42:13.958 --> 03:42:16.405 organoid in the organoid you have

03:42:16.405 --> 03:42:18.865 podocyte you have tubular cell and

03:42:18.940 --> 03:42:21.577 so on and so the first part of the

03:42:21.577 --> 03:42:23.480 study that I showed you with the code.

NOTE Confidence: 0.607870775

03:42:23.480 --> 03:42:26.576 And the COVID was dependent on the organized.

NOTE Confidence: 0.607870775

03:42:26.580 --> 03:42:28.089 The second part,

NOTE Confidence: 0.607870775

03:42:28.089 --> 03:42:29.598 the GEOPATHIC FSGS.

NOTE Confidence: 0.607870775

03:42:29.600 --> 03:42:32.295 Those IPS were directly differentiated

NOTE Confidence: 0.607870775

03:42:32.295 --> 03:42:35.760 to photosite using Samira Moser protocol.

NOTE Confidence: 0.607870775

03:42:35.760 --> 03:42:38.518 So in both cases these were not

NOTE Confidence: 0.607870775

03:42:38.518 --> 03:42:39.700 from the kidney,

NOTE Confidence: 0.607870775

03:42:39.700 --> 03:42:42.330 but these were already programmed.

NOTE Confidence: 0.607870775

03:42:42.330 --> 03:42:43.770 I hope that answers a question.

NOTE Confidence: 0.7657877075

03:42:51.210 --> 03:42:54.252 How do you deal with like

NOTE Confidence: 0.7657877075

03:42:54.252 --> 03:42:55.266 neuronal contamination?

NOTE Confidence: 0.7657877075

03:42:55.270 --> 03:42:57.410 So that's a good question.

NOTE Confidence: 0.7657877075

03:42:57.410 --> 03:42:59.456 So when we actually take this

NOTE Confidence: 0.7657877075

03:42:59.456 --> 03:43:01.232 kidney organized and you look

NOTE Confidence: 0.7657877075

03:43:01.232 --> 03:43:02.967 at the single cell analysis,

NOTE Confidence: 0.7657877075

03:43:02.970 --> 03:43:06.786 you have about 20 sub population.

NOTE Confidence: 0.7657877075

03:43:06.790 --> 03:43:08.776 Think because the role or the

NOTE Confidence: 0.7657877075

03:43:08.776 --> 03:43:11.154 goal of using these I PSC's is

NOTE Confidence: 0.7657877075

03:43:11.154 --> 03:43:13.439 not to transplant into patients.

NOTE Confidence: 0.7657877075

03:43:13.440 --> 03:43:16.320 The goal is for us to actually use a

NOTE Confidence: 0.7657877075

03:43:16.320 --> 03:43:18.844 subset of them, which means the podocyte,

NOTE Confidence: 0.7657877075

03:43:18.844 --> 03:43:19.987 the endothelial cells.

NOTE Confidence: 0.7657877075

03:43:19.990 --> 03:43:22.540 Yes, there is neuronal contamination there,

NOTE Confidence: 0.7657877075

03:43:22.540 --> 03:43:24.577 but it's across from all the patients,

NOTE Confidence: 0.7657877075

03:43:24.580 --> 03:43:26.596 so it's not a perfect tool,

NOTE Confidence: 0.7657877075

03:43:26.600 --> 03:43:28.658 but it's actually, in my view,

NOTE Confidence: 0.7657877075

03:43:28.660 --> 03:43:31.410 actually outperform some of the

NOTE Confidence: 0.7657877075

03:43:31.410 --> 03:43:34.160 immortalized procycling we've been using,

NOTE Confidence: 0.7657877075

03:43:34.160 --> 03:43:38.127 so it's because of the fact that it it

NOTE Confidence: 0.7657877075

03:43:38.127 --> 03:43:41.956 retains the genetic endowment of the patient.

NOTE Confidence: 0.7657877075

03:43:41.960 --> 03:43:42.947 It allows us.

NOTE Confidence: 0.7657877075

03:43:42.947 --> 03:43:47.017 To be able to capture that in a way that we

NOTE Confidence: 0.7657877075

03:43:47.017 --> 03:43:49.543 cannot capture it with immortalized line.

NOTE Confidence: 0.7657877075

03:43:49.550 --> 03:43:52.140 So we actually didn't have to do

NOTE Confidence: 0.7657877075

03:43:52.140 --> 03:43:54.370 with the neuronal contamination,

NOTE Confidence: 0.7657877075

03:43:54.370 --> 03:43:55.135 because that, really,

NOTE Confidence: 0.7657877075

03:43:55.135 --> 03:43:56.920 I don't think that helped with the

NOTE Confidence: 0.7657877075

03:43:56.967 --> 03:43:58.467 question we are trying to answer.

NOTE Confidence: 0.54355174

03:44:00.520 --> 03:44:00.940 So.

NOTE Confidence: 0.8398067

03:44:02.980 --> 03:44:03.370 Don't.

NOTE Confidence: 0.551276974285714

03:44:07.110 --> 03:44:11.387 Really enjoyed it so. You are HIV.

NOTE Confidence: 0.683984595055556

03:44:13.740 --> 03:44:15.846 The patient sample you showed that

NOTE Confidence: 0.683984595055556

03:44:15.846 --> 03:44:18.114 the April one is expressed both

NOTE Confidence: 0.683984595055556

03:44:18.114 --> 03:44:20.490 in the prototypes of the cells.

NOTE Confidence: 0.683984595055556

03:44:20.490 --> 03:44:21.585 Is that something you see

NOTE Confidence: 0.683984595055556

03:44:21.585 --> 03:44:23.020 in all of the models where.

NOTE Confidence: 0.626974818571428

03:44:29.450 --> 03:44:30.890 Genesis The thing is related

NOTE Confidence: 0.626974818571428

03:44:30.890 --> 03:44:32.430 to the support sites versus.

NOTE Confidence: 0.7419567

03:44:34.590 --> 03:44:38.438 Mechanism. Yeah. Did you hear

NOTE Confidence: 0.7419567

03:44:38.438 --> 03:44:40.890 that or I heard the first part?

NOTE Confidence: 0.7419567

03:44:40.890 --> 03:44:42.936 So the employment expression is in

NOTE Confidence: 0.7419567

03:44:42.936 --> 03:44:45.469 the photo site and endothelial cell.

NOTE Confidence: 0.7419567

03:44:45.470 --> 03:44:47.942 How is that? Is that a universal thing

NOTE Confidence: 0.7419567

03:44:47.942 --> 03:44:50.308 for April 1 mediated kidney disease?

NOTE Confidence: 0.7419567

03:44:50.310 --> 03:44:51.000 Is that correct?

NOTE Confidence: 0.805439472857143

03:44:53.160 --> 03:44:57.907 Yes, OK, so we've looked in COVID and

NOTE Confidence: 0.805439472857143

03:44:57.907 --> 03:45:00.523 I will say that in the COVID tissue

NOTE Confidence: 0.805439472857143

03:45:00.523 --> 03:45:03.119 of the nine cases we looked at,

NOTE Confidence: 0.805439472857143

03:45:03.120 --> 03:45:05.878 the answer is the same robust expression

NOTE Confidence: 0.805439472857143

03:45:05.878 --> 03:45:09.021 in the podocyte robust expression in the

NOTE Confidence: 0.805439472857143

03:45:09.021 --> 03:45:12.048 CD 31 positive and the failure cells.

NOTE Confidence: 0.805439472857143

03:45:12.050 --> 03:45:14.722 We are in the process of actually doing

03:45:14.722 --> 03:45:17.347 the same thing with idiopathic FSGS.

03:45:17.350 --> 03:45:19.732 To see. Whether it's also in

03:45:19.732 --> 03:45:21.780 those two compartment as well,

03:45:21.780 --> 03:45:24.476 I can tell it's robustly in the podocyte,

03:45:24.480 --> 03:45:25.296 but we want to do it.

03:45:25.300 --> 03:45:27.136 Careful work to see whether it's

03:45:27.136 --> 03:45:28.760 also in in bethelehem cells,

03:45:28.760 --> 03:45:31.264 but in the COVID for all the cases

03:45:31.264 --> 03:45:33.972 we've looked at, the answer is yes.

03:45:33.972 --> 03:45:36.237 For the endothelial cells and,

03:45:36.240 --> 03:45:37.794 and I think that question from Doctor,

03:45:37.800 --> 03:45:39.672 Babbitt, and that actually

03:45:39.672 --> 03:45:42.012 under score is second question,

03:45:42.020 --> 03:45:44.080 the the understanding of collapsing

03:45:44.080 --> 03:45:46.140 FSGS has been very produced,

NOTE Confidence: 0.805439472857143

03:45:46.140 --> 03:45:48.396 centric, and rightly so.

NOTE Confidence: 0.805439472857143

03:45:48.396 --> 03:45:51.780 But I'm not sure that endothelial

NOTE Confidence: 0.805439472857143

03:45:51.877 --> 03:45:54.597 cells are entirely innocent.

NOTE Confidence: 0.805439472857143

03:45:54.600 --> 03:45:56.130 So hopefully for that work

NOTE Confidence: 0.805439472857143

03:45:56.130 --> 03:45:58.319 will try to to tease that out,

NOTE Confidence: 0.805439472857143

03:45:58.320 --> 03:46:00.474 but I'm not sure whether endothelial

NOTE Confidence: 0.805439472857143

03:46:00.474 --> 03:46:02.369 cells is involving all equal

NOTE Confidence: 0.805439472857143

03:46:02.369 --> 03:46:03.929 1 mediated kidney disease,

NOTE Confidence: 0.805439472857143

03:46:03.930 --> 03:46:06.138 but it appears to be involved

NOTE Confidence: 0.805439472857143

03:46:06.138 --> 03:46:07.870 in COVID in COVID.

NOTE Confidence: 0.842654742222222

03:46:10.110 --> 03:46:13.462 So one question I have is how how

NOTE Confidence: 0.842654742222222

03:46:13.462 --> 03:46:16.672 does increase in April 1 cause

NOTE Confidence: 0.842654742222222

03:46:16.672 --> 03:46:18.948 the toxicity like mechanistically?

NOTE Confidence: 0.842654742222222

03:46:18.950 --> 03:46:20.440 So that's a great question.

NOTE Confidence: 0.842654742222222

03:46:20.440 --> 03:46:25.288 So in our hands we've done a lot

NOTE Confidence: 0.842654742222222

03:46:25.288 --> 03:46:27.616 of overexpression in HK cell.

NOTE Confidence: 0.842654742222222

03:46:27.616 --> 03:46:31.287 One of the first thing we saw was

NOTE Confidence: 0.842654742222222

03:46:31.287 --> 03:46:33.807 that the most proximal phenotype

NOTE Confidence: 0.842654742222222

03:46:33.807 --> 03:46:35.980 was potassium efflux itself.

NOTE Confidence: 0.842654742222222

03:46:35.980 --> 03:46:41.750 I believe that's the gateway upstream.

NOTE Confidence: 0.842654742222222

03:46:41.750 --> 03:46:42.830 Mediator of toxicity.

NOTE Confidence: 0.842654742222222

03:46:42.830 --> 03:46:44.990 There's a lot of controversy here,

NOTE Confidence: 0.842654742222222

03:46:44.990 --> 03:46:48.722 so there's been about 7 different

NOTE Confidence: 0.842654742222222

03:46:48.722 --> 03:46:51.122 mechanism proposed as to how,

NOTE Confidence: 0.842654742222222

03:46:51.122 --> 03:46:53.426 if everybody agree that it's toxic,

NOTE Confidence: 0.842654742222222

03:46:53.430 --> 03:46:55.560 but there are at least seven

NOTE Confidence: 0.842654742222222

03:46:55.560 --> 03:46:56.625 different mechanism proposed.

NOTE Confidence: 0.842654742222222

03:46:56.630 --> 03:46:59.507 My view is that the potassium efflux,

NOTE Confidence: 0.842654742222222

03:46:59.510 --> 03:47:01.827 and in this case also sodium influx,

NOTE Confidence: 0.842654742222222

03:47:01.830 --> 03:47:03.864 is actually central to that we

NOTE Confidence: 0.842654742222222

03:47:03.864 --> 03:47:06.388 are working on trying to to see if

NOTE Confidence: 0.842654742222222

03:47:06.388 --> 03:47:08.407 that if this models will help us

NOTE Confidence: 0.842654742222222

03:47:08.407 --> 03:47:10.249 to clarify that in the knockout

NOTE Confidence: 0.842654742222222

03:47:10.249 --> 03:47:12.055 model I show when we knock.

NOTE Confidence: 0.842654742222222

03:47:12.055 --> 03:47:13.235 Without the fuel one,

NOTE Confidence: 0.842654742222222

03:47:13.240 --> 03:47:14.500 the potassium influx stopped,

NOTE Confidence: 0.842654742222222

03:47:14.500 --> 03:47:16.390 so it's telling us that if

NOTE Confidence: 0.842654742222222

03:47:16.449 --> 03:47:18.419 everyone is self doesn't mediation,

NOTE Confidence: 0.842654742222222

03:47:18.420 --> 03:47:21.598 but they're still contentious at this point.

NOTE Confidence: 0.842654742222222

03:47:21.600 --> 03:47:23.120 So I I think we have to wait.

NOTE Confidence: 0.842654742222222

03:47:23.120 --> 03:47:24.645 There's really not been compelling

NOTE Confidence: 0.842654742222222

03:47:24.645 --> 03:47:27.009 evidence one way or the other that one

NOTE Confidence: 0.842654742222222

03:47:27.009 --> 03:47:29.220 mechanism is superior to the to the other,

NOTE Confidence: 0.842654742222222

03:47:29.220 --> 03:47:31.428 but it's unresolved question.

NOTE Confidence: 0.933717325

03:47:34.920 --> 03:47:36.336 I hope that answers your question.

NOTE Confidence: 0.933717325

03:47:36.340 --> 03:47:38.320 Doctor Shiva that's great.

NOTE Confidence: 0.933647143333333

03:47:44.730 --> 03:47:45.810 Any other questions?

NOTE Confidence: 0.810842718571429

03:47:58.130 --> 03:48:01.014 Have have you compared like interferon alpha,

NOTE Confidence: 0.810842718571429

03:48:01.020 --> 03:48:03.685 gamma and beta in viral

NOTE Confidence: 0.810842718571429

03:48:03.685 --> 03:48:06.920 induced kidney disease? Yeah.

NOTE Confidence: 0.810842718571429

03:48:06.920 --> 03:48:10.890 Yes, so when in that in that graph

NOTE Confidence: 0.810842718571429

03:48:10.890 --> 03:48:13.690 that I showed when you look at the

NOTE Confidence: 0.810842718571429

03:48:13.690 --> 03:48:15.592 effect of the three interference,

NOTE Confidence: 0.810842718571429

03:48:15.592 --> 03:48:18.452 it's actually very convincing that

NOTE Confidence: 0.810842718571429

03:48:18.452 --> 03:48:22.160 interferon gamma has the strongest effect,

NOTE Confidence: 0.810842718571429

03:48:22.160 --> 03:48:25.360 so you see alpha, beta,

NOTE Confidence: 0.810842718571429

03:48:25.360 --> 03:48:28.656 and gamma at least looking both in glomerular

NOTE Confidence: 0.810842718571429

03:48:28.656 --> 03:48:32.650 endothelial cells as well as in podocyte.

NOTE Confidence: 0.810842718571429

03:48:32.650 --> 03:48:36.689 Gamma has the strongest effect in induction,

NOTE Confidence: 0.810842718571429

03:48:36.690 --> 03:48:39.648 followed by beta, followed by Alfred,

NOTE Confidence: 0.810842718571429

03:48:39.650 --> 03:48:42.534 and I should say that this actually

NOTE Confidence: 0.810842718571429

03:48:42.534 --> 03:48:47.470 mimics or confirms what David Friedman

NOTE Confidence: 0.810842718571429

03:48:47.470 --> 03:48:51.145 shown several years ago when he used

NOTE Confidence: 0.810842718571429

03:48:51.145 --> 03:48:53.357 immortalized podocytes that interferon

NOTE Confidence: 0.810842718571429

03:48:53.357 --> 03:48:56.639 gamma for whatever reason has a

NOTE Confidence: 0.810842718571429

03:48:56.639 --> 03:48:57.733 strongest effect.

NOTE Confidence: 0.810842718571429

03:48:57.740 --> 03:49:01.058 In in driving the April 1 expression

NOTE Confidence: 0.810842718571429

03:49:01.060 --> 03:49:03.540 and I also see a question about is

NOTE Confidence: 0.810842718571429

03:49:03.540 --> 03:49:05.888 there on the on the on the chat.

NOTE Confidence: 0.810842718571429

03:49:05.890 --> 03:49:09.265 Is there a well established

NOTE Confidence: 0.810842718571429

03:49:09.265 --> 03:49:11.821 protocol to organize culture

NOTE Confidence: 0.810842718571429

03:49:11.821 --> 03:49:14.329 directly from kidney tissues?

NOTE Confidence: 0.810842718571429

03:49:14.330 --> 03:49:17.468 Just like the way used in

NOTE Confidence: 0.810842718571429

03:49:17.468 --> 03:49:19.560 organic culture and cancer?

NOTE Confidence: 0.810842718571429

03:49:19.560 --> 03:49:21.240 Not that I know of.

NOTE Confidence: 0.810842718571429

03:49:21.240 --> 03:49:23.864 The organoid kidney organoid

NOTE Confidence: 0.810842718571429

03:49:23.864 --> 03:49:27.144 protocols have been more developed

NOTE Confidence: 0.810842718571429

03:49:27.144 --> 03:49:30.184 to go from I PSC's to the organoid.

NOTE Confidence: 0.810842718571429

03:49:30.184 --> 03:49:33.704 I'm not aware of a lot of robust protocol

NOTE Confidence: 0.810842718571429

03:49:33.704 --> 03:49:36.422 for from going from kidney proper.

NOTE Confidence: 0.829307853333333

03:49:38.890 --> 03:49:39.859 To the online.

NOTE Confidence: 0.560273265

03:49:52.770 --> 03:49:54.830 They identified with.

NOTE Confidence: 0.595629531666667

03:49:56.850 --> 03:49:58.368 Don't have yet have to do.

NOTE Confidence: 0.722631994285714

03:50:06.650 --> 03:50:09.272 In in your justice trial is

NOTE Confidence: 0.722631994285714

03:50:09.272 --> 03:50:11.510 there screening for asymptomatic

NOTE Confidence: 0.722631994285714

03:50:11.510 --> 03:50:15.110 people who may happen to have?

NOTE Confidence: 0.722631994285714

03:50:15.110 --> 03:50:19.156 These these risk allele high risk alleles.

NOTE Confidence: 0.722631994285714

03:50:19.160 --> 03:50:21.610 So the the the justice trial is

NOTE Confidence: 0.722631994285714

03:50:21.610 --> 03:50:24.056 only focusing on people who have

NOTE Confidence: 0.722631994285714

03:50:24.056 --> 03:50:26.246 disease who have kidney disease.

NOTE Confidence: 0.722631994285714

03:50:26.250 --> 03:50:28.080 But we have a preceding study,

NOTE Confidence: 0.722631994285714

03:50:28.080 --> 03:50:29.600 we call it darab.

NOTE Confidence: 0.722631994285714

03:50:29.600 --> 03:50:31.880 Duke April 1 research by repository

NOTE Confidence: 0.722631994285714

03:50:31.961 --> 03:50:33.829 where we actually recruit.

NOTE Confidence: 0.722631994285714

03:50:33.830 --> 03:50:36.404 Both people with disease as well

NOTE Confidence: 0.722631994285714

03:50:36.404 --> 03:50:38.735 as healthy volunteers and among

NOTE Confidence: 0.722631994285714

03:50:38.735 --> 03:50:40.867 the edible healthy volunteers.

NOTE Confidence: 0.722631994285714

03:50:40.870 --> 03:50:43.030 We identify people without kidney

NOTE Confidence: 0.722631994285714

03:50:43.030 --> 03:50:44.758 disease with no proteinuria

NOTE Confidence: 0.722631994285714

03:50:44.758 --> 03:50:46.927 and who are age 50 and older.

NOTE Confidence: 0.722631994285714

03:50:46.930 --> 03:50:47.914 What we are doing.

NOTE Confidence: 0.722631994285714

03:50:47.914 --> 03:50:49.827 The goal of that is to actually

NOTE Confidence: 0.722631994285714

03:50:49.827 --> 03:50:52.089 answer the question you are asking.

NOTE Confidence: 0.722631994285714

03:50:52.090 --> 03:50:54.448 If we identify people who are

NOTE Confidence: 0.722631994285714

03:50:54.448 --> 03:50:57.430 healthy carriers and the preliminary

NOTE Confidence: 0.722631994285714

03:50:57.430 --> 03:51:00.350 data from earlier studies,

NOTE Confidence: 0.722631994285714

03:51:00.350 --> 03:51:03.758 what type I showed in the.

NOTE Confidence: 0.722631994285714

03:51:03.760 --> 03:51:05.264 In the heat map,

NOTE Confidence: 0.722631994285714

03:51:05.264 --> 03:51:08.173 we hope to identify enough number of

NOTE Confidence: 0.722631994285714

03:51:08.173 --> 03:51:11.033 healthy carriers and compare their

NOTE Confidence: 0.722631994285714

03:51:11.033 --> 03:51:13.321 transcriptomic and genomic information

NOTE Confidence: 0.722631994285714

03:51:13.400 --> 03:51:15.808 to identify potential modifiers.

NOTE Confidence: 0.722631994285714

03:51:15.810 --> 03:51:16.800 So that's a great question

NOTE Confidence: 0.722631994285714

03:51:16.800 --> 03:51:17.960 and we are working on it.

NOTE Confidence: 0.929415343333333

03:51:22.760 --> 03:51:23.819 Any other questions?

NOTE Confidence: 0.871665032

03:51:27.140 --> 03:51:28.240 Alright, thank you very much.

NOTE Confidence: 0.871665032

03:51:28.240 --> 03:51:30.808 Doctor would be here for a

NOTE Confidence: 0.871665032

03:51:30.808 --> 03:51:32.420 wonderful talk. I got it.

NOTE Confidence: 0.870922644482758

03:51:43.440 --> 03:51:45.491 Well, just wanted to thank all the

NOTE Confidence: 0.870922644482758

03:51:45.491 --> 03:51:47.051 speakers for really a wonderful

NOTE Confidence: 0.870922644482758

03:51:47.051 --> 03:51:48.911 set of talks today and especially

NOTE Confidence: 0.870922644482758

03:51:48.911 --> 03:51:50.510 thank shuda for organizing and

NOTE Confidence: 0.870922644482758

03:51:50.510 --> 03:51:52.358 and knowing about who to invite.

NOTE Confidence: 0.870922644482758

03:51:52.360 --> 03:51:54.080 If you've been left to me we would

364

NOTE Confidence: 0.870922644482758

03:51:54.080 --> 03:51:56.091 have had five talks on proximal tubule

NOTE Confidence: 0.870922644482758

03:51:56.091 --> 03:51:57.616 acidification and I don't think

NOTE Confidence: 0.870922644482758

03:51:57.675 --> 03:51:59.577 anybody would been interested in that.

NOTE Confidence: 0.870922644482758

03:51:59.580 --> 03:52:01.698 So thank you. Shoulda thanked and

NOTE Confidence: 0.870922644482758

03:52:01.698 --> 03:52:03.790 prodotti for helping organize everything.

NOTE Confidence: 0.870922644482758

03:52:03.790 --> 03:52:05.535 Kyle for the Technical Support

NOTE Confidence: 0.870922644482758

03:52:05.535 --> 03:52:07.837 and thank the audience for their

NOTE Confidence: 0.870922644482758

03:52:07.837 --> 03:52:09.797 attention and excellent questions,

NOTE Confidence: 0.870922644482758

03:52:09.800 --> 03:52:12.660 and see everybody next year, hopefully.

NOTE Confidence: 0.870922644482758

03:52:12.660 --> 03:52:14.000 Bye bye.