WEBVTT

00:00:09.600 --> 00:00:11.840 OK, I think we've got a quorum here,

00:00:11.840 --> 00:00:13.317 so we'll go ahead and get started.

00:00:13.320 --> 00:00:15.076 Welcome everyone for joining

00:00:15.076 --> 00:00:16.832 their Perspectives on Medicine

00:00:16.832 --> 00:00:18.240 series February EDITION.

00:00:18.240 --> 00:00:20.936 Hope everyone's staying warm.

00:00:20.936 --> 00:00:23.048 I'm very excited today to introduce

00:00:23.048 --> 00:00:24.998 our speaker for today's session,

00:00:25.000 --> 00:00:26.748 Doctor Akiko Wasaki. Dr.

00:00:26.748 --> 00:00:29.370 Wasaki is the Sterling Professor of

00:00:29.449 --> 00:00:32.439 Immunobiology and Professor of Molecular,

00:00:32.440 --> 00:00:35.128 Cellular and Developmental Biology,

00:00:35.128 --> 00:00:36.865 dermatology, and of epidemiology

00:00:36.865 --> 00:00:38.995 at the Yale School of Medicine,

NOTE Confidence: 0.964983335714286

00:00:39.000 --> 00:00:41.891 and she is also a Principal Investigator

NOTE Confidence: 0.964983335714286

00:00:41.891 --> 00:00:45.119 at the Howard Hughes Medical Institute.

NOTE Confidence: 0.964983335714286

00:00:45.120 --> 00:00:45.792 Long recognizes.

NOTE Confidence: 0.964983335714286

00:00:45.792 --> 00:00:47.472 One of the most distinguished

NOTE Confidence: 0.964983335714286

00:00:47.472 --> 00:00:48.480 and respected immunologists,

NOTE Confidence: 0.964983335714286

00:00:48.480 --> 00:00:50.472 she has helped develop new methods

NOTE Confidence: 0.964983335714286

00:00:50.472 --> 00:00:52.246 of vaccine delivery and contributed

NOTE Confidence: 0.964983335714286

00:00:52.246 --> 00:00:54.191 greatly to our understanding of

NOTE Confidence: 0.964983335714286

00:00:54.191 --> 00:00:56.183 mucosal immunity and the immune

NOTE Confidence: 0.964983335714286

00:00:56.183 --> 00:00:58.439 response to the herpes simplex viruses,

NOTE Confidence: 0.964983335714286

00:00:58.440 --> 00:00:59.342 human rhinovirus,

NOTE Confidence: 0.964983335714286

00:00:59.342 --> 00:01:01.597 Zika virus and most recently

NOTE Confidence: 0.964983335714286

00:01:01.597 --> 00:01:03.800 the SARS COV Two virus.

NOTE Confidence: 0.964983335714286

00:01:03.800 --> 00:01:05.613 Her recent work led to the development

NOTE Confidence: 0.964983335714286

00:01:05.613 --> 00:01:07.849 of a mouse model for COVID-19 and then

NOTE Confidence: 0.964983335714286

00:01:07.849 --> 00:01:09.642 she is also credited with proposing

NOTE Confidence: 0.964983335714286

00:01:09.642 --> 00:01:11.959 hypothesis for the causes of long COVID,

NOTE Confidence: 0.964983335714286

00:01:11.960 --> 00:01:14.225 the post acute squali of

NOTE Confidence: 0.964983335714286

00:01:14.225 --> 00:01:16.037 SARS COVID 2 infection.

NOTE Confidence: 0.964983335714286

00:01:16.040 --> 00:01:17.720 She also currently Co leads the

NOTE Confidence: 0.964983335714286

00:01:17.720 --> 00:01:19.519 Yale Paxilvid for long COVID trial,

NOTE Confidence: 0.964983335714286

00:01:19.520 --> 00:01:21.690 a double-blind randomized control trial

NOTE Confidence: 0.964983335714286

00:01:21.690 --> 00:01:24.293 testing the efficacy of Paxilvid and

NOTE Confidence: 0.964983335714286

00:01:24.293 --> 00:01:26.876 treating people with long COVID alongside Dr.

NOTE Confidence: 0.964983335714286

00:01:26.880 --> 00:01:27.776 Harlan Krumholz.

NOTE Confidence: 0.964983335714286

00:01:27.776 --> 00:01:29.120 But above all,

NOTE Confidence: 0.964983335714286

00:01:29.120 --> 00:01:30.300 her contributions to science,

NOTE Confidence: 0.964983335714286

00:01:30.300 --> 00:01:32.070 which are impossible to cover all

NOTE Confidence: 0.964983335714286

00:01:32.118 --> 00:01:33.964 of them here Doctor Wassaki is a

NOTE Confidence: 0.964983335714286

00:01:33.964 --> 00:01:35.569 beacon of inspiration for women

NOTE Confidence: 0.964983335714286

00:01:35.569 --> 00:01:37.792 in science and a vocal advocate

NOTE Confidence: 0.964983335714286

00:01:37.792 --> 00:01:39.632 for combating sexism in academia.

NOTE Confidence: 0.964983335714286

00:01:39.640 --> 00:01:39.975 Dr.

NOTE Confidence: 0.964983335714286

00:01:39.975 --> 00:01:41.650 Wassaki completed her Bachelor's and

NOTE Confidence: 0.964983335714286

00:01:41.650 --> 00:01:43.668 PhD in immunology at the University

NOTE Confidence: 0.964983335714286

00:01:43.668 --> 00:01:45.516 of Toronto and her post doctorates

NOTE Confidence: 0.964983335714286

00:01:45.516 --> 00:01:47.837 at the National Institutes of Health.

NOTE Confidence: 0.964983335714286

00:01:47.840 --> 00:01:50.150 We're very excited to have her join

NOTE Confidence: 0.964983335714286

00:01:50.150 --> 00:01:53.017 us today on her talk titled The

NOTE Confidence: 0.964983335714286

00:01:53.017 --> 00:01:55.717 Immunology of Post Acute Infection Syndrome.

NOTE Confidence: 0.964983335714286

00:01:55.720 --> 00:01:56.172 Doctor Asaki,

NOTE Confidence: 0.964983335714286

00:01:56.172 --> 00:01:57.754 thank you so much for joining us.

NOTE Confidence: 0.964983335714286

00:01:57.760 --> 00:01:59.335 And I'll turn over to you and

NOTE Confidence: 0.964983335714286

00:01:59.335 --> 00:02:00.360 whenever you are ready.

NOTE Confidence: 0.804083984

00:02:01.320 --> 00:02:03.000 Thank you so much, Wilton.

NOTE Confidence: 0.804083984

00:02:03.000 --> 00:02:05.480 It's really my pleasure to be here today.

NOTE Confidence: 0.804083984

00:02:05.480 --> 00:02:07.545 And I'd like to just give you

NOTE Confidence: 0.804083984

00:02:07.545 --> 00:02:09.127 the most recent update of

NOTE Confidence: 0.804083984

00:02:09.127 --> 00:02:10.999 what we're doing in the lab.

NOTE Confidence: 0.804083984

00:02:11.000 --> 00:02:13.556 So let me share my screen.

NOTE Confidence: 0.846188004

00:02:18.440 --> 00:02:23.080 Can you see this? Yes. OK, great.

NOTE Confidence: 0.846188004

00:02:23.080 --> 00:02:26.014 So yeah, we've been studying many

NOTE Confidence: 0.846188004

00:02:26.014 --> 00:02:28.649 different types of viral infections

NOTE Confidence: 0.846188004

00:02:28.649 --> 00:02:30.644 and thinking about disease

NOTE Confidence: 0.846188004

00:02:30.644 --> 00:02:32.516 pathogenesis of infectious diseases.

NOTE Confidence: 0.846188004

00:02:32.520 --> 00:02:36.148 And so today I'd like to give our current

NOTE Confidence: 0.846188004

00:02:36.148 --> 00:02:38.284 thinking about what may be happening

NOTE Confidence: 0.846188004

00:02:38.284 --> 00:02:40.400 in post acute infection syndromes,

NOTE Confidence: 0.846188004

00:02:40.400 --> 00:02:42.160 which includes long COVID.

NOTE Confidence: 0.883269155384615

00:02:44.240 --> 00:02:47.635 So the this year's theme for the

NOTE Confidence: 0.883269155384615

00:02:47.635 --> 00:02:51.039 seminar series is Shaping the Future,

NOTE Confidence: 0.883269155384615

00:02:51.040 --> 00:02:51.840 Exploring Medicine,

NOTE Confidence: 0.883269155384615

00:02:51.840 --> 00:02:53.440 Research Society and Beyond.

NOTE Confidence: 0.883269155384615

00:02:53.440 --> 00:02:55.960 And I think I'll try to highlight

NOTE Confidence: 0.883269155384615

00:02:55.960 --> 00:02:58.560 how I think our research might

NOTE Confidence: 0.883269155384615

00:02:58.560 --> 00:03:01.680 contribute to this goal of shaping

NOTE Confidence: 0.883269155384615

00:03:01.680 --> 00:03:06.905 the sort of the right kinds of future

NOTE Confidence: 0.883269155384615

00:03:06.905 --> 00:03:09.529 where medicine incorporates patients

NOTE Confidence: 0.883269155384615

00:03:09.529 --> 00:03:11.805 perspective and true collaboration

NOTE Confidence: 0.883269155384615

00:03:11.805 --> 00:03:15.243 with patients to learn about complex

NOTE Confidence: 0.883269155384615

00:03:15.243 --> 00:03:18.321 diseases that are not yet clearly

NOTE Confidence: 0.883269155384615

00:03:18.321 --> 00:03:21.330 understood and how that can contribute

NOTE Confidence: 0.883269155384615

00:03:21.330 --> 00:03:24.927 to both rigor in research as well

NOTE Confidence: 0.883269155384615

00:03:24.927 --> 00:03:27.957 as a diagnosis and therapeutics for

NOTE Confidence: 0.883269155384615

00:03:27.960 --> 00:03:31.520 post acute infection syndromes.

NOTE Confidence: 0.883269155384615

00:03:31.520 --> 00:03:33.720 So before I get there,

NOTE Confidence: 0.883269155384615

00:03:33.720 --> 00:03:36.940 I just wanted to kind of pose this question.

NOTE Confidence: 0.883269155384615

00:03:36.940 --> 00:03:39.040 How do viruses cause disease?

NOTE Confidence: 0.883269155384615

00:03:39.040 --> 00:03:42.048 And I think most of you are probably

NOTE Confidence: 0.883269155384615

00:03:42.048 --> 00:03:44.320 think this is such an obvious

NOTE Confidence: 0.883269155384615

00:03:44.320 --> 00:03:46.318 question what the answer might be,

NOTE Confidence: 0.883269155384615

00:03:46.320 --> 00:03:48.658 but it's a little bit more complicated

NOTE Confidence: 0.883269155384615

00:03:48.658 --> 00:03:50.760 than a simple straight answer.

NOTE Confidence: 0.883269155384615

00:03:50.760 --> 00:03:53.372 We are constantly exposed

NOTE Confidence: 0.883269155384615

00:03:53.372 --> 00:03:55.810 to numerous viral agents,

NOTE Confidence: 0.883269155384615

00:03:55.810 --> 00:03:59.200 not all of them are pathogens.

NOTE Confidence: 0.883269155384615

00:03:59.200 --> 00:04:01.776 Some of them are in fact encoded

NOTE Confidence: 0.883269155384615

00:04:01.776 --> 00:04:02.880 in our genome.

NOTE Confidence: 0.883269155384615

00:04:02.880 --> 00:04:05.838 8% of our genome is occupied

NOTE Confidence: 0.883269155384615

00:04:05.838 --> 00:04:07.317 by endogenous retroviruses,

NOTE Confidence: 0.883269155384615

00:04:07.320 --> 00:04:09.420 seemingly not really causing

NOTE Confidence: 0.883269155384615

00:04:09.420 --> 00:04:11.520 diseases of steady state.

NOTE Confidence: 0.883269155384615

00:04:11.520 --> 00:04:11.988 However,

NOTE Confidence: 0.883269155384615

00:04:11.988 --> 00:04:14.796 we've shown that in the case

NOTE Confidence: 0.883269155384615

00:04:14.796 --> 00:04:16.200 of lupus patients,

NOTE Confidence: 0.883269155384615

00:04:16.200 --> 00:04:19.040 these endogenous retroviral onogens become

NOTE Confidence: 0.883269155384615

00:04:19.040 --> 00:04:21.880 target of pathologic antibody responses.

NOTE Confidence: 0.883269155384615

00:04:21.880 --> 00:04:23.432 And so you know,

NOTE Confidence: 0.883269155384615

00:04:23.432 --> 00:04:24.596 right there are,

NOTE Confidence: 0.883269155384615

00:04:24.600 --> 00:04:26.766 we have this endogenous viruses that

NOTE Confidence: 0.883269155384615

00:04:26.766 --> 00:04:29.238 could be a trigger of autoimmune

NOTE Confidence: 0.883269155384615

00:04:29.238 --> 00:04:31.660 diseases and there are other viruses

NOTE Confidence: 0.883269155384615

00:04:31.660 --> 00:04:34.056 that we occasionally encounter

NOTE Confidence: 0.883269155384615

00:04:34.056 --> 00:04:36.480 through seasonal exposures,

NOTE Confidence: 0.883269155384615

00:04:36.480 --> 00:04:38.452 respiratory infections as well

NOTE Confidence: 0.883269155384615

00:04:38.452 --> 00:04:40.917 as those that we have.

NOTE Confidence: 0.883269155384615

00:04:40.920 --> 00:04:41.672 You know,

NOTE Confidence: 0.883269155384615

00:04:41.672 --> 00:04:44.304 vast majority of us carry as latent

NOTE Confidence: 0.883269155384615

00:04:44.304 --> 00:04:47.440 forms a herpes virus family members.

NOTE Confidence: 0.883269155384615

00:04:47.440 --> 00:04:49.804 So the relationship that we have

NOTE Confidence: 0.883269155384615

00:04:49.804 --> 00:04:52.349 as humans to viruses are you

NOTE Confidence: 0.883269155384615

00:04:52.349 --> 00:04:54.133 know really very dramatically

NOTE Confidence: 0.883269155384615

00:04:54.133 --> 00:04:57.720 between these kinds of agents.

NOTE Confidence: 0.883269155384615

00:04:57.720 --> 00:05:00.738 And so it's possible that the

NOTE Confidence: 0.883269155384615

00:05:00.738 --> 00:05:02.750 viruses are causing disease

NOTE Confidence: 0.883269155384615

00:05:02.847 --> 00:05:05.507 as a result of damage that is

NOTE Confidence: 0.883269155384615

00:05:05.507 --> 00:05:08.240 caused by the viral life cycle.

NOTE Confidence: 0.883269155384615

00:05:08.240 --> 00:05:08.972 For instance,

NOTE Confidence: 0.883269155384615

00:05:08.972 --> 00:05:11.900 if it's a lytic virus that causes a

NOTE Confidence: 0.883269155384615

00:05:11.984 --> 00:05:14.679 license and death of the host cells,

NOTE Confidence: 0.883269155384615

00:05:14.680 --> 00:05:19.755 that would be sufficient to cause disease.

NOTE Confidence: 0.883269155384615

00:05:19.760 --> 00:05:22.712 Whereas if immune response to an

NOTE Confidence: 0.883269155384615

00:05:22.712 --> 00:05:24.680 otherwise innocuous virus infection

NOTE Confidence: 0.883269155384615

00:05:24.761 --> 00:05:27.076 could be triggering the disease.

NOTE Confidence: 0.883269155384615

00:05:27.080 --> 00:05:30.473 An extreme example I gave of the lupus case,

NOTE Confidence: 0.883269155384615

00:05:30.480 --> 00:05:32.964 but there are many other pathogens

NOTE Confidence: 0.883269155384615

00:05:32.964 --> 00:05:36.284 that we may be reacting to overtly

NOTE Confidence: 0.883269155384615

00:05:36.284 --> 00:05:39.504 in a inadvertently or overtly

NOTE Confidence: 0.883269155384615

00:05:39.504 --> 00:05:42.080 to to cause diseases.

NOTE Confidence: 0.883269155384615

00:05:42.080 --> 00:05:44.728 And the real answer to this question is

NOTE Confidence: 0.883269155384615

00:05:44.728 --> 00:05:47.217 likely a combination of these features

NOTE Confidence: 0.883269155384615

00:05:47.217 --> 00:05:49.479 of virus itself causing some damage,

NOTE Confidence: 0.883269155384615

00:05:49.480 --> 00:05:52.288 but then the immune responses that

NOTE Confidence: 0.883269155384615

00:05:52.288 --> 00:05:55.840 are amplifying such pathologies.

NOTE Confidence: 0.883269155384615

00:05:55.840 --> 00:05:59.224 So we've been applying this question

NOTE Confidence: 0.883269155384615

00:05:59.224 --> 00:06:01.960 to multiple pathogens including the

NOTE Confidence: 0.883269155384615

00:06:01.960 --> 00:06:05.800 herpes simplex virus as well as Zika

NOTE Confidence: 0.883269155384615

00:06:05.800 --> 00:06:08.568 virus and rhinovirus and many others.

NOTE Confidence: 0.883269155384615

00:06:08.568 --> 00:06:11.120 And of course when the pandemic hit,

NOTE Confidence: 0.883269155384615

00:06:11.120 --> 00:06:11.760 it was,

NOTE Confidence: 0.883269155384615

00:06:11.760 --> 00:06:12.400 you know,

NOTE Confidence: 0.883269155384615

00:06:12.400 --> 00:06:15.264 we were in a in a perfect situation

NOTE Confidence: 0.883269155384615

00:06:15.264 --> 00:06:18.096 to be addressing how does SARS

NOTE Confidence: 0.883269155384615

00:06:18.096 --> 00:06:21.158 COV two infection cause disease.

NOTE Confidence: 0.883269155384615

00:06:21.160 --> 00:06:24.625 And this question has been sort of

NOTE Confidence: 0.883269155384615

00:06:24.625 --> 00:06:26.895 tackled by numerous laboratories

NOTE Confidence: 0.883269155384615

00:06:26.895 --> 00:06:28.959 around the world.

NOTE Confidence: 0.883269155384615

00:06:28.960 --> 00:06:31.998 And the current insights that we have

NOTE Confidence: 0.883269155384615

00:06:32.000 --> 00:06:35.960 is essentially a sequence of event

NOTE Confidence: 0.883269155384615

00:06:35.960 --> 00:06:38.396 that leads to severe acute disease.

NOTE Confidence: 0.883269155384615

00:06:38.400 --> 00:06:42.408 And this happens most dominantly in

NOTE Confidence: 0.883269155384615

00:06:42.408 --> 00:06:46.480 older adults and males over females.

NOTE Confidence: 0.945101850555556

00:06:46.480 --> 00:06:48.844 And what's happening here is that

NOTE Confidence: 0.945101850555556

00:06:48.844 --> 00:06:51.300 there is starting off with an

NOTE Confidence: 0.945101850555556

00:06:51.300 --> 00:06:53.718 inability to mount a timely response.

NOTE Confidence: 0.945101850555556

00:06:53.720 --> 00:06:58.208 This happens due to aging due to

NOTE Confidence: 0.945101850555556

00:06:58.208 --> 00:07:01.246 delayed interferon response as a

NOTE Confidence: 0.945101850555556

00:07:01.246 --> 00:07:04.384 result of having genetic lesions in

NOTE Confidence: 0.945101850555556

00:07:04.384 --> 00:07:07.226 these pathways or having impaired

NOTE Confidence: 0.945101850555556

00:07:07.226 --> 00:07:10.238 on neutralizing antibody responses.

NOTE Confidence: 0.945101850555556

00:07:10.240 --> 00:07:12.350 And this leads to replication

NOTE Confidence: 0.945101850555556

00:07:12.350 --> 00:07:14.460 and persistence of virus that

NOTE Confidence: 0.945101850555556

00:07:14.539 --> 00:07:16.759 sees multiple different organs,

NOTE Confidence: 0.945101850555556

00:07:16.760 --> 00:07:19.208 including the obviously from the lung

NOTE Confidence: 0.945101850555556

00:07:19.208 --> 00:07:21.497 but including many other organs.

NOTE Confidence: 0.945101850555556

00:07:21.497 --> 00:07:25.954 And it's really the excess myelopoiesis and

NOTE Confidence: 0.945101850555556

00:07:25.954 --> 00:07:29.426 release of these myeloid cells that are,

NOTE Confidence: 0.945101850555556

00:07:29.426 --> 00:07:31.356 you know, 'cause vascular damage,

NOTE Confidence: 0.945101850555556

00:07:31.360 --> 00:07:34.528 leakiness as well as blood clot

NOTE Confidence: 0.945101850555556

00:07:34.528 --> 00:07:36.112 and tissue damage,

NOTE Confidence: 0.945101850555556

00:07:36.120 --> 00:07:39.636 leading to severe cases of COVID.

NOTE Confidence: 0.945101850555556

00:07:39.640 --> 00:07:43.133 And so the the world of scientists

NOTE Confidence: 0.945101850555556

00:07:43.133 --> 00:07:45.657 really got together and figured

NOTE Confidence: 0.945101850555556

00:07:45.657 --> 00:07:47.600 out small pieces of this puzzle.

NOTE Confidence: 0.945101850555556

00:07:47.600 --> 00:07:49.514 And now we kind of have a pretty

NOTE Confidence: 0.945101850555556

00:07:49.514 --> 00:07:51.878 good idea of what's going on.

NOTE Confidence: 0.945101850555556

00:07:51.880 --> 00:07:54.752 And having this kind of insight at the

NOTE Confidence: 0.945101850555556

00:07:54.752 --> 00:07:56.661 cellular and molecular level really

NOTE Confidence: 0.945101850555556

00:07:56.661 --> 00:07:59.821 help the field to come up with an

NOTE Confidence: 0.945101850555556

00:07:59.821 --> 00:08:01.729 appropriate therapeutic modalities to

NOTE Confidence: 0.945101850555556

00:08:01.729 --> 00:08:05.000 target each of these defective pathways.

NOTE Confidence: 0.954532728

00:08:07.400 --> 00:08:08.840 And why is this important?

NOTE Confidence: 0.954532728

00:08:08.840 --> 00:08:11.012 To really think about? How does

NOTE Confidence: 0.954532728

00:08:11.012 --> 00:08:13.040 an infectious agent cause disease?

NOTE Confidence: 0.947581818

00:08:15.160 --> 00:08:17.520 To treat an infectious disease,

NOTE Confidence: 0.947581818

00:08:17.520 --> 00:08:19.345 we really need to understand

NOTE Confidence: 0.947581818

00:08:19.345 --> 00:08:21.170 which of the scenarios is

NOTE Confidence: 0.947581818

00:08:21.245 --> 00:08:23.477 responsible for the pathogenesis,

NOTE Confidence: 0.947581818

00:08:23.480 --> 00:08:25.600 because depending on that answer,

NOTE Confidence: 0.947581818

00:08:25.600 --> 00:08:27.820 the treatment strategy will greatly

NOTE Confidence: 0.947581818

00:08:27.820 --> 00:08:30.040 differ based on that knowledge.

NOTE Confidence: 0.947581818

00:08:30.040 --> 00:08:31.426 For instance, do we want to

NOTE Confidence: 0.947581818

00:08:31.426 --> 00:08:33.109 target the virus or do we want

NOTE Confidence: 0.947581818

00:08:33.109 --> 00:08:34.279 to target the immune cells?

NOTE Confidence: 0.947581818

00:08:34.280 --> 00:08:37.115 And if So, what part of the immune cells,

NOTE Confidence: 0.947581818

00:08:37.120 --> 00:08:40.480 the immune system should we be going

NOTE Confidence: 0.947581818

00:08:40.480 --> 00:08:42.736 after and also finding unexpected

NOTE Confidence: 0.947581818

00:08:42.736 --> 00:08:44.956 causes of disease will dramatically

NOTE Confidence: 0.947581818

00:08:44.956 --> 00:08:47.119 change the way we treat patients.

NOTE Confidence: 0.947581818

00:08:47.120 --> 00:08:47.968 For instance,

NOTE Confidence: 0.947581818

00:08:47.968 --> 00:08:50.926 the most recent and strong evidence

NOTE Confidence: 0.947581818

00:08:50.926 --> 00:08:54.298 linking Epstein Barr virus to multiple

NOTE Confidence: 0.947581818

00:08:54.298 --> 00:08:57.324 sclerosis and and systemic lupus

NOTE Confidence: 0.947581818

00:08:57.324 --> 00:08:59.666 erythematosis really, you know,

NOTE Confidence: 0.947581818

00:08:59.666 --> 00:09:02.576 makes us think differently about

NOTE Confidence: 0.947581818

00:09:02.576 --> 00:09:05.199 prevention of these diseases.

NOTE Confidence: 0.947581818

00:09:05.200 --> 00:09:07.120 So there's a lot of good reasons why

NOTE Confidence: 0.947581818

00:09:07.120 --> 00:09:09.079 we need to be thinking about this.

NOTE Confidence: 0.945119679285714

00:09:11.600 --> 00:09:14.111 But today I want to focus on this post

NOTE Confidence: 0.945119679285714

00:09:14.111 --> 00:09:16.240 acute phase of infectious disease,

NOTE Confidence: 0.945119679285714

00:09:16.240 --> 00:09:18.480 which is really these medically

NOTE Confidence: 0.945119679285714

00:09:18.480 --> 00:09:20.720 unexplained chronic diseases that happen

NOTE Confidence: 0.945119679285714

00:09:20.720 --> 00:09:24.200 after a number of different infections.

NOTE Confidence: 0.945119679285714

00:09:24.200 --> 00:09:26.756 And right now the, you know,

NOTE Confidence: 0.945119679285714

00:09:26.760 --> 00:09:30.960 underlying mechanisms is unclear.

NOTE Confidence: 0.945119679285714

00:09:30.960 --> 00:09:33.330 But it's important to note that

NOTE Confidence: 0.945119679285714

00:09:33.330 --> 00:09:36.095 there are number of infectious agents

NOTE Confidence: 0.945119679285714

00:09:36.095 --> 00:09:38.845 that can cause these unexplained

NOTE Confidence: 0.945119679285714

00:09:38.845 --> 00:09:41.280 post acute infection syndrome,

NOTE Confidence: 0.945119679285714

00:09:41.280 --> 00:09:43.680 including many viruses, Ebola,

NOTE Confidence: 0.945119679285714

00:09:43.680 --> 00:09:46.320 dengue, Poliosaurus, chikunya ebb,

NOTE Confidence: 0.945119679285714

00:09:46.320 --> 00:09:49.800 many others, as well as some

NOTE Confidence: 0.945119679285714

00:09:49.800 --> 00:09:51.920 bacterial and parasitic pathogens.

NOTE Confidence: 0.945119679285714

00:09:51.920 --> 00:09:54.557 And this is a review that I had the

NOTE Confidence: 0.945119679285714

00:09:54.557 --> 00:09:57.316 fortune of riding together with Yan Chokka,

NOTE Confidence: 0.945119679285714

00:09:57.320 --> 00:10:01.598 who himself is an MECFS patient.

NOTE Confidence: 0.945119679285714

00:10:01.600 --> 00:10:04.678 And this is one of the examples in which,

NOTE Confidence: 0.945119679285714

00:10:04.680 --> 00:10:06.912 you know, as I was saying in the beginning,

NOTE Confidence: 0.945119679285714

00:10:06.920 --> 00:10:10.100 how do we kind of plot out the

NOTE Confidence: 0.945119679285714

00:10:10.100 --> 00:10:11.480 future of medicine?

NOTE Confidence: 0.945119679285714

00:10:11.480 --> 00:10:13.200 It really requires collaboration,

NOTE Confidence: 0.945119679285714

00:10:13.200 --> 00:10:15.350 a true collaboration and learning

NOTE Confidence: 0.945119679285714

00:10:15.350 --> 00:10:17.279 from the patients themselves,

NOTE Confidence: 0.945119679285714

00:10:17.280 --> 00:10:20.728 who many of them are experts in the

NOTE Confidence: 0.945119679285714

00:10:20.728 --> 00:10:22.200 diseases that they're suffering from.

NOTE Confidence: 0.81263163875

00:10:24.760 --> 00:10:26.885 So what are these post

NOTE Confidence: 0.81263163875

00:10:26.885 --> 00:10:28.160 acute infection syndromes?

NOTE Confidence: 0.81263163875

00:10:28.160 --> 00:10:30.620 There are over 200 symptoms

NOTE Confidence: 0.81263163875

00:10:30.620 --> 00:10:33.080 reported for long COVID alone,

NOTE Confidence: 0.81263163875

00:10:33.080 --> 00:10:35.396 but there are some core symptoms

NOTE Confidence: 0.81263163875

00:10:35.396 --> 00:10:37.549 that most of these patients

NOTE Confidence: 0.81263163875

00:10:37.549 --> 00:10:40.212 share which are listed here.

NOTE Confidence: 0.81263163875

00:10:40.212 --> 00:10:41.278 Exertional intolerance,

NOTE Confidence: 0.81263163875

00:10:41.280 --> 00:10:45.501 severe fatigue and many of these symptoms

NOTE Confidence: 0.81263163875

00:10:45.501 --> 00:10:48.360 also involve neurocognitive impairment,

NOTE Confidence: 0.81263163875

00:10:48.360 --> 00:10:49.768 sensory impairment,

NOTE Confidence: 0.81263163875

00:10:49.768 --> 00:10:51.880 flu like symptoms,

NOTE Confidence: 0.81263163875

00:10:51.880 --> 00:10:52.750 sleep disturbances.

NOTE Confidence: 0.81263163875

00:10:52.750 --> 00:10:56.809 This is one of the major things that happen

NOTE Confidence: 0.81263163875

00:10:56.809 --> 00:10:59.310 in these place conditions Dysautonomia,

NOTE Confidence: 0.81263163875

00:10:59.310 --> 00:11:00.330 myalgia, arthralgia.

NOTE Confidence: 0.81263163875

00:11:00.330 --> 00:11:03.390 These are some of the main

NOTE Confidence: 0.81263163875

00:11:03.390 --> 00:11:06.076 sort of symptoms that are being

NOTE Confidence: 0.81263163875

00:11:06.076 --> 00:11:08.180 reported by people regardless of

NOTE Confidence: 0.81263163875

00:11:08.180 --> 00:11:10.280 how the disease was triggered.

NOTE Confidence: 0.854498064545455

00:11:13.000 --> 00:11:16.832 And the reality of these Long post Acute

NOTE Confidence: 0.854498064545455

00:11:16.832 --> 00:11:19.030 infection syndrome is quite serious.

NOTE Confidence: 0.854498064545455

00:11:19.030 --> 00:11:22.495 It's estimated that a 65 million people

NOTE Confidence: 0.854498064545455

00:11:22.495 --> 00:11:26.076 in the world are currently living with

NOTE Confidence: 0.854498064545455

00:11:26.076 --> 00:11:29.910 long COVID and about 20 million people

NOTE Confidence: 0.854498064545455

00:11:29.910 --> 00:11:32.174 with my Myalgic encephalomyelitis

NOTE Confidence: 0.854498064545455

00:11:32.174 --> 00:11:35.040 or Chronic Fatigue syndrome,

NOTE Confidence: 0.854498064545455

00:11:35.040 --> 00:11:39.513 25% of whom are bed bound or house bound.

NOTE Confidence: 0.854498064545455

00:11:39.520 --> 00:11:42.976 And any CFS can strike people of all ages

NOTE Confidence: 0.854498064545455

00:11:42.976 --> 00:11:46.357 and backgrounds and so can long COVID.

NOTE Confidence: 0.854498064545455

00:11:46.360 --> 00:11:50.488 And what what we do know is that it does

NOTE Confidence: 0.854498064545455

00:11:50.488 --> 00:11:55.160 strike people of female sex as well as

NOTE Confidence: 0.854498064545455

00:11:55.160 --> 00:12:00.680 ages between 30 to 50 more dominantly

NOTE Confidence: 0.854498064545455

00:12:00.680 --> 00:12:03.080 than in other demographic groups.

NOTE Confidence: 0.854498064545455

00:12:03.080 --> 00:12:06.052 But it doesn't mean that people outside

NOTE Confidence: 0.854498064545455

00:12:06.052 --> 00:12:09.255 of that cannot be susceptible to this.

NOTE Confidence: 0.854498064545455

00:12:09.255 --> 00:12:12.050 So it's really a problem that's

NOTE Confidence: 0.854498064545455

00:12:12.050 --> 00:12:15.080 plaguing the world right now and

NOTE Confidence: 0.854498064545455

00:12:15.080 --> 00:12:20.520 not only is the labor workforce and

NOTE Confidence: 0.854498064545455

00:12:20.520 --> 00:12:22.240 my schools are being impacted,

NOTE Confidence: 0.854498064545455

00:12:22.240 --> 00:12:24.480 but also becoming a social,

NOTE Confidence: 0.854498064545455

00:12:24.480 --> 00:12:27.936 economic and national security

NOTE Confidence: 0.854498064545455

00:12:27.936 --> 00:12:30.872 problem because it impacts everyone.

NOTE Confidence: 0.854498064545455

00:12:30.872 --> 00:12:34.320 It you know obviously shortage in the

NOTE Confidence: 0.854498064545455

00:12:34.320 --> 00:12:37.722 national security issues labor force will

NOTE Confidence: 0.854498064545455

00:12:37.722 --> 00:12:42.437 be a problem for World Peace I would say.

NOTE Confidence: 0.854498064545455

00:12:42.440 --> 00:12:44.757 So this is something that I think

NOTE Confidence: 0.854498064545455

00:12:44.757 --> 00:12:47.143 the world needs to pay more attention

NOTE Confidence: 0.854498064545455

00:12:47.143 --> 00:12:49.604 to and start to really put some

NOTE Confidence: 0.854498064545455

00:12:49.604 --> 00:12:52.820 resources to try to figure this out and

NOTE Confidence: 0.854498064545455

00:12:52.908 --> 00:12:57.720 provide therapeutics and diagnostics.

NOTE Confidence: 0.854498064545455

00:12:57.720 --> 00:13:00.400 So as a basic scientist,

NOTE Confidence: 0.854498064545455

00:13:00.400 --> 00:13:03.046 you know we are thinking about four

NOTE Confidence: 0.854498064545455

00:13:03.046 --> 00:13:05.000 possible root causes of disease.

NOTE Confidence: 0.854498064545455

00:13:05.000 --> 00:13:07.832 There are many sort of downstream

NOTE Confidence: 0.854498064545455

00:13:07.832 --> 00:13:10.915 pathologies that you find such as clotting

NOTE Confidence: 0.854498064545455

00:13:10.915 --> 00:13:14.800 issues or muscle damage and so on.

NOTE Confidence: 0.854498064545455

00:13:14.800 --> 00:13:17.397 But what is actually driving these diseases?

NOTE Confidence: 0.854498064545455

00:13:17.400 --> 00:13:19.359 The root causes.

NOTE Confidence: 0.854498064545455

00:13:19.360 --> 00:13:22.480 So we I listed four of them here.

NOTE Confidence: 0.854498064545455

00:13:22.480 --> 00:13:24.406 Viral reservoir of SARS COV two

NOTE Confidence: 0.854498064545455

00:13:24.406 --> 00:13:26.720 could be one of them for long.

NOTE Confidence: 0.854498064545455

00:13:26.720 --> 00:13:29.010 COVID autoimmunity that involves T

NOTE Confidence: 0.854498064545455

00:13:29.010 --> 00:13:31.790 cells and antibodies may be another

NOTE Confidence: 0.854498064545455

00:13:31.790 --> 00:13:34.639 one that can be triggered triggered as

NOTE Confidence: 0.854498064545455

00:13:34.639 --> 00:13:37.440 a result of SARS, COV two infection,

NOTE Confidence: 0.854498064545455

00:13:37.440 --> 00:13:39.200 tissue damage and dysfunction,

NOTE Confidence: 0.854498064545455

00:13:39.200 --> 00:13:43.360 and latent viral reactivation.

NOTE Confidence: 0.854498064545455

00:13:43.360 --> 00:13:44.636 As I mentioned earlier,

NOTE Confidence: 0.854498064545455

00:13:44.636 --> 00:13:46.550 we are all colonized with the

NOTE Confidence: 0.854498064545455

00:13:46.618 --> 00:13:49.006 number of viruses which are mostly

NOTE Confidence: 0.854498064545455

00:13:49.006 --> 00:13:50.598 latent and healthy individuals,

NOTE Confidence: 0.854498064545455

00:13:50.600 --> 00:13:54.440 but these these viruses can reactivate.

NOTE Confidence: 0.854498064545455

00:13:54.440 --> 00:13:57.360 So based on these hypotheses,

NOTE Confidence: 0.854498064545455

00:13:57.360 --> 00:14:00.097 we are now using every tools under

NOTE Confidence: 0.854498064545455

00:14:00.097 --> 00:14:03.360 the sun to try to figure out what,

NOTE Confidence: 0.854498064545455

00:14:03.360 --> 00:14:04.260 if any,

NOTE Confidence: 0.854498064545455

00:14:04.260 --> 00:14:06.510 of these root causes might

NOTE Confidence: 0.854498064545455

00:14:06.510 --> 00:14:08.820 be resulting in long COVID.

NOTE Confidence: 0.854498064545455

00:14:08.820 --> 00:14:12.255 And I'll give you snippets of several

NOTE Confidence: 0.854498064545455

00:14:12.255 --> 00:14:14.355 different studies to illustrate

NOTE Confidence: 0.854498064545455

00:14:14.360 --> 00:14:17.276 evidence for each of these hypothesis.

NOTE Confidence: 0.854498064545455

00:14:17.280 --> 00:14:20.472 So this first study is a Mount Sinai

NOTE Confidence: 0.854498064545455

00:14:20.472 --> 00:14:23.601 Yale long COVID study where I have

NOTE Confidence: 0.854498064545455

00:14:23.601 --> 00:14:25.736 the fortune of collaborating with

NOTE Confidence: 0.854498064545455

00:14:25.736 --> 00:14:28.495 Doctor David Petrino who sees patients

NOTE Confidence: 0.854498064545455

00:14:28.495 --> 00:14:31.568 thousands of patients with long COVID and

NOTE Confidence: 0.854498064545455

00:14:31.568 --> 00:14:34.192 he's at the Mount Sinai School of Medicine.

NOTE Confidence: 0.854498064545455

00:14:34.200 --> 00:14:36.148 These team members, Jamie,

NOTE Confidence: 0.854498064545455

00:14:36.148 --> 00:14:38.096 Laura and Dana contributed

NOTE Confidence: 0.854498064545455

00:14:38.096 --> 00:14:39.840 significantly to the study.

NOTE Confidence: 0.854498064545455

00:14:39.840 --> 00:14:43.096 And on the Yale side, John Klein,

NOTE Confidence: 0.854498064545455

00:14:43.096 --> 00:14:46.953 who some of you may know is an MDPHD

NOTE Confidence: 0.854498064545455

00:14:46.953 --> 00:14:50.382 student about to to graduate Rahul,

NOTE Confidence: 0.854498064545455

00:14:50.382 --> 00:14:54.078 he was an MD student here at Yale.

NOTE Confidence: 0.854498064545455

00:14:54.080 --> 00:14:57.302 He's already gone to presidency in California

NOTE Confidence: 0.854498064545455

00:14:57.302 --> 00:15:00.840 pay when a post doctor fell on the lab.

NOTE Confidence: 0.854498064545455

00:15:00.840 --> 00:15:02.199 Jill J Cox,

NOTE Confidence: 0.854498064545455

00:15:02.199 --> 00:15:04.917 a graduate MSDP student here at

NOTE Confidence: 0.854498064545455

00:15:04.917 --> 00:15:07.358 Yale in Aaron Ring's lab.

NOTE Confidence: 0.854498064545455

00:15:07.360 --> 00:15:08.184 Jeff Gelhausen,

NOTE Confidence: 0.854498064545455

00:15:08.184 --> 00:15:11.480 he is a dermatology fellow in my lab.

NOTE Confidence: 0.759773883636364

00:15:11.480 --> 00:15:12.548 And Sasha Tabachnikova,

NOTE Confidence: 0.759773883636364

00:15:12.548 --> 00:15:15.360 she is a graduate student in the lab,

NOTE Confidence: 0.759773883636364

00:15:15.360 --> 00:15:18.288 And David Van **** also contributed

NOTE Confidence: 0.759773883636364

00:15:18.288 --> 00:15:19.752 his computational approaches.

NOTE Confidence: 0.759773883636364

00:15:19.760 --> 00:15:23.144 And Aaron Ring developed this rapid

NOTE Confidence: 0.759773883636364

00:15:23.144 --> 00:15:24.836 extracellular antigen profiling,

NOTE Confidence: 0.759773883636364

00:15:24.840 --> 00:15:26.925 which we used to identify

NOTE Confidence: 0.759773883636364

00:15:26.925 --> 00:15:27.759 antibody reactivity.

NOTE Confidence: 0.892299935

00:15:30.160 --> 00:15:31.704 So in this study,

NOTE Confidence: 0.892299935

00:15:31.704 --> 00:15:35.288 we've recruited five sets of participants,

NOTE Confidence: 0.892299935

00:15:35.288 --> 00:15:37.394 long COVID participants,

NOTE Confidence: 0.892299935

00:15:37.400 --> 00:15:39.048 99 people convalescent control.

NOTE Confidence: 0.892299935

00:15:39.048 --> 00:15:41.923 These are the people who got COVID

NOTE Confidence: 0.892299935

00:15:41.923 --> 00:15:44.233 around the same time as those who

NOTE Confidence: 0.892299935

00:15:44.233 --> 00:15:46.677 got long COVID but then recovered.

NOTE Confidence: 0.892299935

00:15:46.680 --> 00:15:49.403 We have 39 healthy controls who weren't

NOTE Confidence: 0.892299935

00:15:49.403 --> 00:15:51.917 infected at the time of the study.

NOTE Confidence: 0.892299935

00:15:51.920 --> 00:15:54.644 There are also healthcare workers from

NOTE Confidence: 0.892299935

00:15:54.644 --> 00:15:57.513 Yale that contributed blood for a vaccine

NOTE Confidence: 0.892299935

00:15:57.513 --> 00:16:00.160 study and external long COVID participants.

NOTE Confidence: 0.892299935

00:16:00.160 --> 00:16:03.360 These are the patients that are seen by

NOTE Confidence: 0.892299935

00:16:03.360 --> 00:16:06.520 the Yale Pulmonary long COVID Clinic.

NOTE Confidence: 0.892299935

00:16:06.520 --> 00:16:11.320 And so we collected their blood and analyzed

NOTE Confidence: 0.892299935

00:16:11.320 --> 00:16:15.520 variety of factors including cell subsets,

NOTE Confidence: 0.892299935

00:16:15.520 --> 00:16:18.600 activation status using full cytometry,

NOTE Confidence: 0.892299935

00:16:18.600 --> 00:16:22.266 looking at linear epitope mapping using

NOTE Confidence: 0.892299935

00:16:22.266 --> 00:16:25.960 serumen psoroscovie 2 antigen profiling,

NOTE Confidence: 0.892299935

00:16:25.960 --> 00:16:27.296 peptide display, oh sorry,

NOTE Confidence: 0.892299935

00:16:27.296 --> 00:16:29.300 this is the the saramine peptide

NOTE Confidence: 0.892299935

00:16:29.364 --> 00:16:31.094 display library and the human

NOTE Confidence: 0.892299935

00:16:31.094 --> 00:16:33.229 extraprotium library is the one that

NOTE Confidence: 0.892299935

00:16:33.229 --> 00:16:35.317 I mentioned that Aaron Ring developed.

NOTE Confidence: 0.892299935

00:16:35.320 --> 00:16:39.457 And then proteomics of plasma as

NOTE Confidence: 0.892299935

00:16:39.457 --> 00:16:41.719 well as EMR and symptom survey.

NOTE Confidence: 0.892299935

00:16:41.720 --> 00:16:44.714 And combining these things we did

NOTE Confidence: 0.892299935

00:16:44.714 --> 00:16:47.280 find significant changes in immune

NOTE Confidence: 0.892299935

00:16:47.280 --> 00:16:50.160 profiles of those with long COVID.

NOTE Confidence: 0.892299935

00:16:50.160 --> 00:16:52.785 First, the types of participants

NOTE Confidence: 0.892299935

00:16:52.785 --> 00:16:54.360 that were recruited.

NOTE Confidence: 0.892299935

00:16:54.360 --> 00:16:57.228 We're the age group of about

NOTE Confidence: 0.892299935

00:16:57.228 --> 00:17:00.040 30 to 50 years of age.

NOTE Confidence: 0.892299935

00:17:00.040 --> 00:17:01.090 That's the the,

NOTE Confidence: 0.892299935

00:17:01.090 --> 00:17:03.540 the most sort of high risk factor

NOTE Confidence: 0.892299935

00:17:03.611 --> 00:17:06.005 group that that are seen by the

NOTE Confidence: 0.892299935

00:17:06.005 --> 00:17:08.039 Mount Sinai long COVID clinic.

NOTE Confidence: 0.892299935

00:17:08.040 --> 00:17:11.615 We have dominantly female participants

NOTE Confidence: 0.892299935

00:17:11.615 --> 00:17:15.860 and again this Pais and long COVID

NOTE Confidence: 0.892299935

00:17:15.860 --> 00:17:17.960 are female dominant disease.

NOTE Confidence: 0.892299935

00:17:17.960 --> 00:17:21.404 We also focused on acute severity that

NOTE Confidence: 0.892299935

00:17:21.404 --> 00:17:23.668 was not hospitalized because vast

NOTE Confidence: 0.892299935

00:17:23.668 --> 00:17:26.032 majority of people with long COVID

NOTE Confidence: 0.892299935

00:17:26.032 --> 00:17:28.797 were not hospitalized to begin with.

NOTE Confidence: 0.892299935

00:17:28.800 --> 00:17:31.600 And then based from acute COVID were

NOTE Confidence: 0.892299935

00:17:31.600 --> 00:17:34.640 were around 400 days plus or minus.

NOTE Confidence: 0.892299935

00:17:34.640 --> 00:17:37.466 So this is a much later time point than

NOTE Confidence: 0.892299935

00:17:37.466 --> 00:17:40.159 other studies that have been published.

NOTE Confidence: 0.892299935

00:17:40.160 --> 00:17:42.398 Looking at the full cytometry data,

NOTE Confidence: 0.892299935

00:17:42.400 --> 00:17:46.740 we identified that there are increases

NOTE Confidence: 0.892299935

00:17:46.740 --> 00:17:49.640 in non conventional monocyte populations.

NOTE Confidence: 0.892299935

00:17:49.640 --> 00:17:52.670 In people with long COVID we have

NOTE Confidence: 0.892299935

00:17:52.670 --> 00:17:54.410 reduction in circulating dendritic

NOTE Confidence: 0.892299935

00:17:54.410 --> 00:17:55.715 cell type one.

NOTE Confidence: 0.892299935

00:17:55.720 --> 00:17:58.527 These are the cells that are very

NOTE Confidence: 0.892299935

00:17:58.527 --> 00:18:01.060 important for priming T cell immune

NOTE Confidence: 0.892299935

00:18:01.060 --> 00:18:03.105 responses and we see increased activation

NOTE Confidence: 0.892299935

00:18:03.105 --> 00:18:05.840 of B cells and double negative B cells.

NOTE Confidence: 0.917394692

00:18:08.480 --> 00:18:09.520 On the T cell side,

NOTE Confidence: 0.917394692

00:18:09.520 --> 00:18:13.520 we see reduced circulating tissue,

NOTE Confidence: 0.917394692

00:18:13.520 --> 00:18:16.920 central memory T cells of the CD4 type,

NOTE Confidence: 0.917394692

00:18:16.920 --> 00:18:20.480 as well as increases in exhausted T cells.

NOTE Confidence: 0.917394692

00:18:20.480 --> 00:18:23.516 And another study from UCSF identified

NOTE Confidence: 0.917394692

00:18:23.516 --> 00:18:26.039 that this increase in exhausted

NOTE Confidence: 0.917394692

00:18:26.039 --> 00:18:28.916 T cells are seen in SARS COV,

NOTE Confidence: 0.917394692

00:18:28.920 --> 00:18:30.912 two specific T cells,

NOTE Confidence: 0.917394692

00:18:30.912 --> 00:18:33.402 so suggestive of persistent virus

NOTE Confidence: 0.917394692

00:18:33.402 --> 00:18:35.959 driving the Exhaustion phenotype.

NOTE Confidence: 0.815007008333333

00:18:38.480 --> 00:18:41.720 We also saw an increases in

NOTE Confidence: 0.815007008333333

00:18:41.720 --> 00:18:43.520 cytokine secretion from T

NOTE Confidence: 0.815007008333333

00:18:43.520 --> 00:18:45.320 cells including Illinois 2,

NOTE Confidence: 0.815007008333333

00:18:45.320 --> 00:18:47.360 Illinois four and Illinois 6.

NOTE Confidence: 0.815007008333333

00:18:47.360 --> 00:18:49.300 And long COVID participants were

00:18:49.300 --> 00:18:51.533 pretty much the only people who

00:18:51.533 --> 00:18:53.200 had diesels that secreted both

00:18:53.200 --> 00:18:55.000 Illinois four and Illinois 6.

00:18:57.680 --> 00:19:01.920 Looking at the long COVID patients is

00:19:01.920 --> 00:19:05.760 antibody responses to SARS COV 2 antigens.

00:19:05.760 --> 00:19:09.309 We noticed that the anti spike antibodies

00:19:09.309 --> 00:19:12.300 were elevated in those with long

00:19:12.300 --> 00:19:15.388 COVID whether we looked at the whole

00:19:15.388 --> 00:19:18.959 spike at the S1 region or the RBD.

00:19:18.960 --> 00:19:21.288 So this suggested that there again

00:19:21.288 --> 00:19:24.453 there may be a viral reservoir that's

00:19:24.453 --> 00:19:27.513 driving the increases in these anti

00:19:27.520 --> 00:19:29.544 antiviral antibodies over time.

00:19:29.544 --> 00:19:32.854 Notice that there is a mark X2.

00:19:32.854 --> 00:19:35.563 This denotes the fact that we only

00:19:35.563 --> 00:19:38.528 included participants who had two doses

NOTE Confidence: 0.96933747

00:19:38.528 --> 00:19:41.890 of mRNA vaccine just to remove any impact

NOTE Confidence: 0.96933747

00:19:41.890 --> 00:19:44.678 of the vaccines in what the antibodies

NOTE Confidence: 0.96933747

00:19:44.678 --> 00:19:47.674 that we're you know looking at here.

NOTE Confidence: 0.96933747

00:19:47.680 --> 00:19:50.551 So T cell site and B cell site are

NOTE Confidence: 0.96933747

00:19:50.551 --> 00:19:53.188 telling us that there may be a SARS

NOTE Confidence: 0.96933747

00:19:53.188 --> 00:19:55.926 Scooby 2 viral reservoir that may be

NOTE Confidence: 0.96933747

00:19:55.926 --> 00:19:58.280 driving a chronic immune responses

NOTE Confidence: 0.931757338571429

00:20:00.440 --> 00:20:02.440 when we looked at the

NOTE Confidence: 0.931757338571429

00:20:02.440 --> 00:20:03.916 levels of plasma factors.

NOTE Confidence: 0.931757338571429

00:20:03.916 --> 00:20:06.620 So the way in which you read this

NOTE Confidence: 0.931757338571429

00:20:06.695 --> 00:20:09.127 graph is to look at the the right

NOTE Confidence: 0.931757338571429

00:20:09.127 --> 00:20:11.264 side which is elevated in people

NOTE Confidence: 0.931757338571429

00:20:11.264 --> 00:20:13.880 with long COVID and you see things

NOTE Confidence: 0.931757338571429

00:20:13.880 --> 00:20:16.362 like complement C4B elevated and

NOTE Confidence: 0.931757338571429

00:20:16.362 --> 00:20:18.658 several different chemokines and

NOTE Confidence: 0.931757338571429

00:20:18.658 --> 00:20:21.480 cytokines that are upregulated.

NOTE Confidence: 0.931757338571429

00:20:21.480 --> 00:20:23.940 Whereas one factor that really stood

NOTE Confidence: 0.931757338571429

00:20:23.940 --> 00:20:27.199 out for us was the cortisol level.

NOTE Confidence: 0.931757338571429

00:20:27.200 --> 00:20:30.368 So cortisol level was almost uniformly

NOTE Confidence: 0.931757338571429

00:20:30.368 --> 00:20:33.520 reduced in people with long COVID,

NOTE Confidence: 0.931757338571429

00:20:33.520 --> 00:20:36.190 and there's also slight reduction of

NOTE Confidence: 0.931757338571429

00:20:36.190 --> 00:20:39.696 Illinois 5 S The cortisol was by far

NOTE Confidence: 0.931757338571429

00:20:39.696 --> 00:20:41.684 the most impressively different factor

NOTE Confidence: 0.931757338571429

00:20:41.684 --> 00:20:43.880 that we find in the people with long COVID,

NOTE Confidence: 0.931757338571429

00:20:43.880 --> 00:20:46.330 and this is sort of AZ score

NOTE Confidence: 0.931757338571429

00:20:46.330 --> 00:20:47.800 representation of that data.

NOTE Confidence: 0.931757338571429

00:20:47.800 --> 00:20:49.800 So the long COVID participants

NOTE Confidence: 0.931757338571429

00:20:49.800 --> 00:20:51.400 had much lower levels,

NOTE Confidence: 0.931757338571429

00:20:51.400 --> 00:20:55.040 almost half of the level of cortisol

NOTE Confidence: 0.931757338571429

00:20:55.040 --> 00:20:58.240 in compared to healthy controls.

NOTE Confidence: 0.931757338571429

00:20:58.240 --> 00:21:00.536 And of course cortisol is the urinal

NOTE Confidence: 0.931757338571429

00:21:00.536 --> 00:21:02.956 hormone and we wanted to ensure that

NOTE Confidence: 0.931757338571429

00:21:02.956 --> 00:21:05.486 the time of collection of blood from

NOTE Confidence: 0.931757338571429

00:21:05.486 --> 00:21:07.546 these participants were similar and

NOTE Confidence: 0.931757338571429

00:21:07.546 --> 00:21:11.455 indeed they were pretty similar people.

NOTE Confidence: 0.931757338571429

00:21:11.455 --> 00:21:11.950 So.

NOTE Confidence: 0.931757338571429

00:21:11.950 --> 00:21:14.920 So because this was quite striking,

NOTE Confidence: 0.931757338571429

00:21:14.920 --> 00:21:17.295 we wanted to validate this

NOTE Confidence: 0.931757338571429

00:21:17.295 --> 00:21:19.195 finding in another cohort.

NOTE Confidence: 0.931757338571429

00:21:19.200 --> 00:21:21.992 And so we looked at the blood of

NOTE Confidence: 0.931757338571429

00:21:21.992 --> 00:21:24.619 this Yale Pulmonary Clinic patients

NOTE Confidence: 0.931757338571429

00:21:24.619 --> 00:21:27.694 and they also exhibited significant

NOTE Confidence: 0.931757338571429

00:21:27.694 --> 00:21:30.920 reduction in the levels of cortisol.

NOTE Confidence: 0.944594672857143

00:21:33.320 --> 00:21:37.275 So cortisol is a very important hormone.

NOTE Confidence: 0.944594672857143

00:21:37.280 --> 00:21:39.604 It's known as a stress hormone but

NOTE Confidence: 0.944594672857143

00:21:39.604 --> 00:21:42.006 it's actually very important for the

NOTE Confidence: 0.944594672857143

00:21:42.006 --> 00:21:44.176 physiological functioning of the of

NOTE Confidence: 0.944594672857143

00:21:44.176 --> 00:21:47.184 the of the Organism on a daily basis

NOTE Confidence: 0.944594672857143

00:21:47.184 --> 00:21:50.667 and it's regulated by the central

NOTE Confidence: 0.944594672857143

00:21:50.667 --> 00:21:53.079 hypothalamic and pituitary axis.

NOTE Confidence: 0.944594672857143

00:21:53.080 --> 00:21:56.020 Hypothalamus secrets the CRH which

NOTE Confidence: 0.944594672857143

00:21:56.020 --> 00:21:58.400 then trigger ACTH secretion from

NOTE Confidence: 0.944594672857143

00:21:58.400 --> 00:22:01.200 the pituitary which then acts on the

NOTE Confidence: 0.944594672857143

00:22:01.271 --> 00:22:03.411 adrenal glands to produce cortisol

NOTE Confidence: 0.944594672857143

00:22:03.411 --> 00:22:06.200 which then has a negative feedback

NOTE Confidence: 0.944594672857143

00:22:06.200 --> 00:22:10.960 regulation of these upstream hormones.

NOTE Confidence: 0.944594672857143

00:22:10.960 --> 00:22:14.838 So we wanted to understand whether the

NOTE Confidence: 0.944594672857143

00:22:14.840 --> 00:22:17.384 there was any kind of impact of having

NOTE Confidence: 0.944594672857143

00:22:17.384 --> 00:22:20.720 long COVID on the adrenal hormone ACTH level.

NOTE Confidence: 0.944594672857143

00:22:20.720 --> 00:22:24.080 And we thought that because the

NOTE Confidence: 0.944594672857143

00:22:24.180 --> 00:22:26.740 level of the cortisol is so much

NOTE Confidence: 0.944594672857143

00:22:26.740 --> 00:22:28.515 lower than the healthy control,

NOTE Confidence: 0.944594672857143

00:22:28.520 --> 00:22:31.292 it would expect an elevated level of

NOTE Confidence: 0.944594672857143

00:22:31.292 --> 00:22:33.920 ACTH to compensate for that low level,

NOTE Confidence: 0.944594672857143

00:22:33.920 --> 00:22:36.755 but that's not what we saw here.

NOTE Confidence: 0.944594672857143

00:22:36.760 --> 00:22:39.562 So this suggests that there may

NOTE Confidence: 0.944594672857143

00:22:39.562 --> 00:22:42.535 be a central dysregulation of the

NOTE Confidence: 0.944594672857143

00:22:42.535 --> 00:22:45.075 hypothalamus pituitary axis and that's

NOTE Confidence: 0.944594672857143

00:22:45.075 --> 00:22:48.059 something that we are now investigating

NOTE Confidence: 0.944594672857143

00:22:48.059 --> 00:22:51.272 using MRI and other models that the

NOTE Confidence: 0.944594672857143

00:22:51.280 --> 00:22:52.800 animal models that we're creating.

NOTE Confidence: 0.91237346375

00:22:55.080 --> 00:22:58.330 So what about the latent

NOTE Confidence: 0.91237346375

00:22:58.330 --> 00:23:00.280 viral reactivation hypothesis?

NOTE Confidence: 0.91237346375

00:23:00.280 --> 00:23:03.800 To this end, we looked at the antibody

NOTE Confidence: 0.91237346375

00:23:03.800 --> 00:23:05.780 reactivity against lytic proteins

NOTE Confidence: 0.91237346375

00:23:05.780 --> 00:23:08.320 of herpes virus family members.

NOTE Confidence: 0.91237346375

00:23:08.320 --> 00:23:11.104 And what we noted is that there is

NOTE Confidence: 0.91237346375

00:23:11.104 --> 00:23:13.571 an elevated level of IgG against

NOTE Confidence: 0.91237346375

00:23:13.571 --> 00:23:16.592 Epstein Barr virus onnogens P23 and

NOTE Confidence: 0.91237346375

00:23:16.592 --> 00:23:20.096 GP42 as well as varicella zoster

NOTE Confidence: 0.91237346375

00:23:20.096 --> 00:23:24.076 virus GE in patients with long COVID.

NOTE Confidence: 0.91237346375

00:23:24.080 --> 00:23:26.672 And and and this difference cannot

NOTE Confidence: 0.91237346375

00:23:26.672 --> 00:23:31.880 be accounted for by the latent virus

NOTE Confidence: 0.91237346375

00:23:31.880 --> 00:23:34.841 status in these people because when we

NOTE Confidence: 0.91237346375

00:23:34.841 --> 00:23:38.400 looked at the chronic or latent antigens,

NOTE Confidence: 0.91237346375

00:23:38.400 --> 00:23:41.460 antibody reactivity were equal between

NOTE Confidence: 0.91237346375

00:23:41.460 --> 00:23:44.520 controls and long COVID participants.

NOTE Confidence: 0.91237346375

00:23:44.520 --> 00:23:47.026 So this really suggested that there may

NOTE Confidence: 0.91237346375

00:23:47.026 --> 00:23:49.550 have been a recent reactivation of EVV

NOTE Confidence: 0.91237346375

00:23:49.550 --> 00:23:52.600 and VCV in a subset of participants.

NOTE Confidence: 0.91237346375

00:23:52.600 --> 00:23:55.558 And since we reported this study,

NOTE Confidence: 0.91237346375

00:23:55.560 --> 00:23:58.248 there have been two other studies

NOTE Confidence: 0.91237346375

00:23:58.248 --> 00:24:01.004 that have confirmed EBB reactivation

NOTE Confidence: 0.91237346375

00:24:01.004 --> 00:24:04.514 in patients with long COVID.

NOTE Confidence: 0.91237346375

00:24:04.520 --> 00:24:07.496 So the long COVID patients here

NOTE Confidence: 0.91237346375

00:24:07.496 --> 00:24:09.480 again are in purple.

NOTE Confidence: 0.91237346375

00:24:09.480 --> 00:24:12.309 This is the REAP score that illustrates

NOTE Confidence: 0.91237346375

00:24:12.309 --> 00:24:15.363 how much higher the antibody levels

NOTE Confidence: 0.91237346375

00:24:15.363 --> 00:24:18.266 are in people with long COVID

NOTE Confidence: 0.91237346375

00:24:18.266 --> 00:24:21.972 against the ebb P23 and and.

NOTE Confidence: 0.91237346375

00:24:21.972 --> 00:24:24.254 But we use two other types of

NOTE Confidence: 0.91237346375

00:24:24.254 --> 00:24:25.718 approaches to confirm this.

NOTE Confidence: 0.91237346375

00:24:25.720 --> 00:24:29.082 One is to look at the the ceremian,

NOTE Confidence: 0.91237346375

00:24:29.082 --> 00:24:31.687 the linear epitope mapping strategy

NOTE Confidence: 0.91237346375

00:24:31.687 --> 00:24:35.365 to map a particular epitope the

NOTE Confidence: 0.91237346375

00:24:35.365 --> 00:24:39.076 peptide within the GP 42 of EBV.

NOTE Confidence: 0.91237346375

00:24:39.080 --> 00:24:42.232 And here again you see that increase

NOTE Confidence: 0.91237346375

00:24:42.232 --> 00:24:45.816 in the Z score for this antibody

NOTE Confidence: 0.91237346375

00:24:45.816 --> 00:24:49.532 in patients with on COVID BZ Beach.

NOTE Confidence: 0.91237346375

00:24:49.532 --> 00:24:53.960 GE is similarly elevated for reactivity.

NOTE Confidence: 0.91237346375

00:24:53.960 --> 00:24:58.760 And curiously the the EBB reactive antibody

NOTE Confidence: 0.91237346375

00:24:58.760 --> 00:25:02.000 score correlated positively with Illinois 4,

NOTE Confidence: 0.91237346375

00:25:02.000 --> 00:25:04.256 Illinois 6 double positive CD4T cells

NOTE Confidence: 0.91237346375

00:25:04.256 --> 00:25:06.903 which I showed you is pretty much

NOTE Confidence: 0.91237346375

00:25:06.903 --> 00:25:09.395 only present in those with long COVID.

NOTE Confidence: 0.91237346375

00:25:09.400 --> 00:25:11.710 So whether there's a functional link

NOTE Confidence: 0.91237346375

00:25:11.710 --> 00:25:13.688 between the the cytokine secreting

NOTE Confidence: 0.91237346375

00:25:13.688 --> 00:25:16.250 T cells and the antibody score as

NOTE Confidence: 0.91237346375

00:25:16.250 --> 00:25:18.319 something that we're investigating.

NOTE Confidence: 0.783886338333333

00:25:21.680 --> 00:25:26.280 And so with David Van **** and Rahul,

NOTE Confidence: 0.783886338333333

00:25:26.280 --> 00:25:29.822 they they looked at the our immunological

NOTE Confidence: 0.783886338333333

00:25:29.822 --> 00:25:32.812 phenotyping and determined that a handful

NOTE Confidence: 0.783886338333333

00:25:32.812 --> 00:25:35.770 of immune factors alone can distinguish

NOTE Confidence: 0.783886338333333

00:25:35.850 --> 00:25:38.885 people with long COVID with 94% accuracy.

NOTE Confidence: 0.783886338333333

00:25:38.885 --> 00:25:42.070 And those factors turned out to be

NOTE Confidence: 0.783886338333333

00:25:42.161 --> 00:25:45.425 things like cortisol reduced levels of

NOTE Confidence: 0.783886338333333

00:25:45.425 --> 00:25:48.515 CD4TCM and dendritic cell type one,

NOTE Confidence: 0.783886338333333

00:25:48.520 --> 00:25:52.278 as well as increased levels of EBB GP42,

NOTE Confidence: 0.783886338333333

00:25:52.278 --> 00:25:54.190 reactive antibody and Galactin

NOTE Confidence: 0.783886338333333

00:25:54.190 --> 00:25:57.721 one and a handful of other sort

NOTE Confidence: 0.783886338333333

00:25:57.721 --> 00:26:00.356 of cellular and cytokine markers.

NOTE Confidence: 0.783886338333333

00:26:00.360 --> 00:26:02.782 So this really kind of painted the

NOTE Confidence: 0.783886338333333

00:26:02.782 --> 00:26:06.305 picture that long COVID can be explained

NOTE Confidence: 0.783886338333333

00:26:06.305 --> 00:26:08.467 by immunological perturbations and

NOTE Confidence: 0.783886338333333

00:26:08.467 --> 00:26:09.868 endocrinological perturbations alone.

NOTE Confidence: 0.783886338333333

00:26:09.868 --> 00:26:13.427 And this is something that we really need

NOTE Confidence: 0.783886338333333

00:26:13.427 --> 00:26:16.163 to pay attention to with respect to both

NOTE Confidence: 0.783886338333333

00:26:16.234 --> 00:26:19.000 biomarker for diagnosis and for treatment.

NOTE Confidence: 0.904039466153846

00:26:21.240 --> 00:26:23.648 So we took the same set of data

NOTE Confidence: 0.904039466153846

00:26:23.648 --> 00:26:25.799 and now asked the question,

NOTE Confidence: 0.904039466153846

00:26:25.800 --> 00:26:27.912 what are the sex differences in

NOTE Confidence: 0.904039466153846

00:26:27.912 --> 00:26:29.954 long COVID immune phenotype, if any?

NOTE Confidence: 0.904039466153846

00:26:29.954 --> 00:26:32.923 And this is a work done by Julio Silva

NOTE Confidence: 0.904039466153846

00:26:32.923 --> 00:26:35.805 who is a current MDPHD student here,

NOTE Confidence: 0.904039466153846

00:26:35.805 --> 00:26:39.126 and Takahira Takahashi who's a former postdoc

NOTE Confidence: 0.904039466153846

00:26:39.126 --> 00:26:43.160 who who now runs his own lab in Japan.

NOTE Confidence: 0.904039466153846

00:26:43.160 --> 00:26:45.316 So taking the same set of data,

NOTE Confidence: 0.904039466153846

00:26:45.320 --> 00:26:47.903 we are now dividing people into male

NOTE Confidence: 0.904039466153846

00:26:47.903 --> 00:26:49.944 versus female and control versus

NOTE Confidence: 0.904039466153846

00:26:49.944 --> 00:26:52.864 long COVID and applying some machine

NOTE Confidence: 0.904039466153846

00:26:52.864 --> 00:26:55.960 learning analysis to understand you know

NOTE Confidence: 0.904039466153846

00:26:56.043 --> 00:26:58.527 what are the the different features

NOTE Confidence: 0.904039466153846

00:26:58.527 --> 00:27:01.519 that are found in these two sexes.

NOTE Confidence: 0.904039466153846

00:27:01.520 --> 00:27:03.837 So females with long COVID A females

NOTE Confidence: 0.904039466153846

00:27:03.837 --> 00:27:06.040 here are always indicated in blue,

NOTE Confidence: 0.904039466153846

00:27:06.040 --> 00:27:08.320 males are in red.

NOTE Confidence: 0.904039466153846

00:27:08.320 --> 00:27:10.546 You can see that the symptom burden

NOTE Confidence: 0.904039466153846

00:27:10.546 --> 00:27:13.065 is higher in females with long COVID

NOTE Confidence: 0.904039466153846

00:27:13.065 --> 00:27:15.180 compared to the males and organ

NOTE Confidence: 0.904039466153846

00:27:15.180 --> 00:27:16.730 system involvement is also higher

NOTE Confidence: 0.904039466153846

00:27:16.730 --> 00:27:18.917 in the female compared to the males.

NOTE Confidence: 0.866044454

00:27:21.920 --> 00:27:24.265 This is a very interesting

NOTE Confidence: 0.866044454

00:27:24.265 --> 00:27:26.610 chart showing that the distinct

NOTE Confidence: 0.866044454

00:27:26.691 --> 00:27:29.436 symptoms affect males and females.

NOTE Confidence: 0.866044454

00:27:29.440 --> 00:27:32.415 So at the top, the relative frequency

NOTE Confidence: 0.866044454

00:27:32.415 --> 00:27:34.966 of symptoms such as sleep and

NOTE Confidence: 0.866044454

00:27:34.966 --> 00:27:37.796 disorientation and urinary issues are

NOTE Confidence: 0.866044454

00:27:37.796 --> 00:27:41.160 equally reported in males and females.

NOTE Confidence: 0.866044454

00:27:41.160 --> 00:27:43.386 However, if you go down this list

NOTE Confidence: 0.866044454

00:27:43.386 --> 00:27:45.240 further and further on the bottom,

NOTE Confidence: 0.866044454

00:27:45.240 --> 00:27:47.960 here are female dominance symptoms.

NOTE Confidence: 0.866044454

00:27:47.960 --> 00:27:50.670 That includes things like dizziness

NOTE Confidence: 0.866044454

00:27:50.670 --> 00:27:53.173 and body temperature issues, throat,

NOTE Confidence: 0.866044454

00:27:53.173 --> 00:27:54.838 chest pain, pins and needles,

NOTE Confidence: 0.866044454

00:27:54.840 --> 00:27:57.759 and so on, which is more frequently

NOTE Confidence: 0.866044454

00:27:57.759 --> 00:27:59.920 reported in females over males.

NOTE Confidence: 0.866044454

00:27:59.920 --> 00:28:03.160 And the most sexually dimorphic

NOTE Confidence: 0.866044454

00:28:03.160 --> 00:28:06.400 symptom was the sexual dysfunction

NOTE Confidence: 0.866044454

00:28:06.498 --> 00:28:09.634 in male and hair loss in female.

NOTE Confidence: 0.866044454

00:28:09.640 --> 00:28:13.033 So this this alone tells us that people

NOTE Confidence: 0.866044454

00:28:13.033 --> 00:28:15.398 are experiencing long COVID differently,

NOTE Confidence: 0.866044454

00:28:15.400 --> 00:28:19.328 that based on their biological sex and that

NOTE Confidence: 0.866044454

00:28:19.328 --> 00:28:21.876 there may be different drivers of disease.

NOTE Confidence: 0.95721841

00:28:24.720 --> 00:28:27.400 Looking at the immune features,

NOTE Confidence: 0.95721841

00:28:27.400 --> 00:28:30.040 we saw things like the exhausted

NOTE Confidence: 0.95721841

00:28:30.040 --> 00:28:31.800 T cells being elevated,

NOTE Confidence: 0.95721841

00:28:31.800 --> 00:28:35.680 particularly in the female cohort.

NOTE Confidence: 0.95721841

00:28:35.680 --> 00:28:38.482 Females with bone COVID and cytokine

NOTE Confidence: 0.95721841

00:28:38.482 --> 00:28:40.905 secreting T cells were also

NOTE Confidence: 0.95721841

00:28:40.905 --> 00:28:43.718 dominantly in females with bone COVID.

NOTE Confidence: 0.95721841

00:28:43.718 --> 00:28:45.470 Ebb reactive antibodies were

NOTE Confidence: 0.95721841

00:28:45.470 --> 00:28:48.075 also found mostly in females with

NOTE Confidence: 0.95721841

00:28:48.075 --> 00:28:49.936 bone COVID indicating that those

NOTE Confidence: 0.95721841

00:28:49.936 --> 00:28:52.680 features that I showed you just a

NOTE Confidence: 0.95721841

00:28:52.760 --> 00:28:54.610 few slides ago that distinguished

NOTE Confidence: 0.95721841

00:28:54.610 --> 00:28:56.735 male distinguished long COVID versus

NOTE Confidence: 0.95721841

00:28:56.735 --> 00:28:59.342 non long COVID that many of them

NOTE Confidence: 0.95721841

00:28:59.342 --> 00:29:01.238 are driven by the female patients.

NOTE Confidence: 0.92151599

00:29:03.640 --> 00:29:06.658 Males also do have differences in

NOTE Confidence: 0.92151599

00:29:06.658 --> 00:29:08.670 their immune features including

NOTE Confidence: 0.92151599

00:29:08.755 --> 00:29:11.079 elevated natural killer cells,

NOTE Confidence: 0.92151599

00:29:11.080 --> 00:29:12.728 TGF beta and April.

NOTE Confidence: 0.92151599

00:29:12.728 --> 00:29:15.200 These are cytokine levels that are

NOTE Confidence: 0.92151599

00:29:15.200 --> 00:29:17.756 higher in males with long COVID.

NOTE Confidence: 0.914068403333333

00:29:21.000 --> 00:29:24.535 And then when we looked at different

NOTE Confidence: 0.914068403333333

00:29:24.535 --> 00:29:26.879 hormones that are circulating

NOTE Confidence: 0.914068403333333

00:29:26.879 --> 00:29:29.799 in patients versus control,

NOTE Confidence: 0.914068403333333

00:29:29.800 --> 00:29:32.100 obviously testosterone is much higher

NOTE Confidence: 0.914068403333333

00:29:32.100 --> 00:29:35.439 in males compared to the females here.

NOTE Confidence: 0.914068403333333

00:29:35.440 --> 00:29:38.114 But what you know is that the

NOTE Confidence: 0.914068403333333

00:29:38.120 --> 00:29:40.592 females with long COVID have lower

NOTE Confidence: 0.914068403333333

00:29:40.592 --> 00:29:42.240 levels of testosterone compared

NOTE Confidence: 0.914068403333333

00:29:42.308 --> 00:29:44.120 to their healthy counterpart.

NOTE Confidence: 0.914068403333333

00:29:44.120 --> 00:29:46.880 And this is interesting because testosterone,

NOTE Confidence: 0.914068403333333

00:29:46.880 --> 00:29:48.700 even though it's mostly thought

NOTE Confidence: 0.914068403333333

00:29:48.700 --> 00:29:50.520 of as a male hormone,

NOTE Confidence: 0.914068403333333

00:29:50.520 --> 00:29:53.685 has important physiological function in

NOTE Confidence: 0.914068403333333

00:29:53.685 --> 00:29:56.240 females and reduced levels of testosterone.

NOTE Confidence: 0.914068403333333

00:29:56.240 --> 00:29:58.150 Testosterone could be leading to

NOTE Confidence: 0.914068403333333

00:29:58.150 --> 00:30:00.630 some of the symptoms that people

NOTE Confidence: 0.914068403333333

00:30:00.630 --> 00:30:03.698 are experiencing and doing this

NOTE Confidence: 0.914068403333333

00:30:03.698 --> 00:30:05.756 logistic regression analysis.

NOTE Confidence: 0.914068403333333

00:30:05.760 --> 00:30:09.477 Accounting for HDMI and other Co founders,

NOTE Confidence: 0.914068403333333

00:30:09.480 --> 00:30:12.112 we noted that the test the per

NOTE Confidence: 0.914068403333333

00:30:12.112 --> 00:30:14.241 unit changes in the testosterone

NOTE Confidence: 0.914068403333333

00:30:14.241 --> 00:30:17.447 is the top factor that can predict

NOTE Confidence: 0.914068403333333

00:30:17.447 --> 00:30:20.277 long COVID status within females.

NOTE Confidence: 0.851759821304348

00:30:22.600 --> 00:30:25.379 And conversely, we see that males have

NOTE Confidence: 0.851759821304348

00:30:25.379 --> 00:30:27.540 lower levels of estradiol compared

NOTE Confidence: 0.851759821304348

00:30:27.540 --> 00:30:30.228 to males with long COVID compared

NOTE Confidence: 0.851759821304348

00:30:30.228 --> 00:30:33.038 to their control male counterpart.

NOTE Confidence: 0.851759821304348

00:30:33.040 --> 00:30:36.680 And estradiol per unit change

NOTE Confidence: 0.851759821304348

00:30:36.680 --> 00:30:39.500 is again the top predictor of

NOTE Confidence: 0.851759821304348

00:30:39.500 --> 00:30:42.040 long COVID status in males,

NOTE Confidence: 0.851759821304348

00:30:42.040 --> 00:30:43.760 which is better than say,

NOTE Confidence: 0.851759821304348

00:30:43.760 --> 00:30:45.280 something like cortisol here.

NOTE Confidence: 0.76380296375

00:30:47.600 --> 00:30:50.480 So this already told us that there's a

NOTE Confidence: 0.76380296375

00:30:50.480 --> 00:30:53.114 very big difference between the sexes

NOTE Confidence: 0.76380296375

00:30:53.114 --> 00:30:55.960 with respect to EBV reactivation,

NOTE Confidence: 0.76380296375

00:30:55.960 --> 00:30:59.200 the cytokine secreting T cells and NK cells,

NOTE Confidence: 0.76380296375

00:30:59.200 --> 00:31:01.385 as well as hormonal changes

NOTE Confidence: 0.76380296375

00:31:01.385 --> 00:31:04.280 that are seen in these people.

NOTE Confidence: 0.76380296375

00:31:04.280 --> 00:31:06.597 And I haven't said much about autoimmunity,

NOTE Confidence: 0.76380296375

00:31:06.600 --> 00:31:11.568 but so when we use the read to identify

NOTE Confidence: 0.76380296375

00:31:11.568 --> 00:31:13.688 broadly what patients might be

NOTE Confidence: 0.76380296375

00:31:13.688 --> 00:31:16.400 reacting to with respect to their IgG,

NOTE Confidence: 0.76380296375

00:31:16.400 --> 00:31:20.369 we did not see a public auto antigen that

NOTE Confidence: 0.76380296375

00:31:20.369 --> 00:31:24.080 like everyone in long COVID group had.

NOTE Confidence: 0.76380296375

00:31:24.080 --> 00:31:27.600 However, we didn't give up.

NOTE Confidence: 0.76380296375

00:31:27.600 --> 00:31:29.976 We, meaning Kayla, saw a postdoc

NOTE Confidence: 0.76380296375

00:31:29.976 --> 00:31:32.280 who's very talented in the lump,

NOTE Confidence: 0.76380296375

00:31:32.280 --> 00:31:35.424 decided to do a functional experiment

NOTE Confidence: 0.76380296375

00:31:35.424 --> 00:31:39.358 where she purified IgG from healthy people,

NOTE Confidence: 0.76380296375

00:31:39.360 --> 00:31:40.707 homeless and control,

NOTE Confidence: 0.76380296375

00:31:40.707 --> 00:31:42.503 severe acute COVID patients

NOTE Confidence: 0.76380296375

00:31:42.503 --> 00:31:44.560 and long COVID patients,

NOTE Confidence: 0.76380296375

00:31:44.560 --> 00:31:48.277 and possibly transfer these into B6 mice.

NOTE Confidence: 0.76380296375

00:31:48.280 --> 00:31:50.590 And she did a battery of behavioral

NOTE Confidence: 0.76380296375

00:31:50.590 --> 00:31:55.120 tests to look at anxiety and

NOTE Confidence: 0.76380296375

00:31:55.120 --> 00:31:57.465 other sort of behavioral issues

NOTE Confidence: 0.76380296375

00:31:57.465 --> 00:32:00.320 that we could measure in mice.

NOTE Confidence: 0.902299638

00:32:02.360 --> 00:32:03.840 She did many, many tests,

NOTE Confidence: 0.902299638

00:32:03.840 --> 00:32:06.112 but I'm only going to show you what's

NOTE Confidence: 0.902299638

00:32:06.112 --> 00:32:09.640 different in the recipients of these animals.

NOTE Confidence: 0.902299638

00:32:09.640 --> 00:32:13.476 One thing Kayla found was that the

NOTE Confidence: 0.902299638

00:32:13.476 --> 00:32:16.620 balance and coordination of mice that

NOTE Confidence: 0.902299638

00:32:16.620 --> 00:32:19.620 are injected with IgG from patients

NOTE Confidence: 0.902299638

00:32:19.620 --> 00:32:23.240 from with long COVID were quite reduced.

NOTE Confidence: 0.902299638

00:32:23.240 --> 00:32:27.216 So this is a rotorod analysis where you

NOTE Confidence: 0.902299638

00:32:27.216 --> 00:32:30.292 let the mice hang on to this rotating

NOTE Confidence: 0.902299638

00:32:30.292 --> 00:32:33.280 rod and the mice have to kind of keep

NOTE Confidence: 0.902299638

00:32:33.353 --> 00:32:35.873 balanced in order to hang on to it.

NOTE Confidence: 0.902299638

00:32:35.880 --> 00:32:37.000 When they lose balance,

NOTE Confidence: 0.902299638

00:32:37.000 --> 00:32:38.680 they fall off and the latency

NOTE Confidence: 0.902299638

00:32:38.741 --> 00:32:39.956 to fall is measured in.

NOTE Confidence: 0.902299638

00:32:39.960 --> 00:32:43.623 Here you can see that the PBS or the

NOTE Confidence: 0.902299638

00:32:43.623 --> 00:32:46.584 healthy control IgG injected animals were

NOTE Confidence: 0.902299638

00:32:46.584 --> 00:32:50.864 able to hang on for 200 seconds or so.

NOTE Confidence: 0.902299638

00:32:50.864 --> 00:32:53.288 However, those who were injected

NOTE Confidence: 0.902299638

00:32:53.288 --> 00:32:56.240 with IgG from long COVID patients

NOTE Confidence: 0.902299638

00:32:56.326 --> 00:32:59.152 had a much reduced latency to fall,

NOTE Confidence: 0.902299638

00:32:59.152 --> 00:33:00.848 indicating that auto antibodies

NOTE Confidence: 0.902299638

00:33:00.848 --> 00:33:03.044 are sufficient to induce loss

NOTE Confidence: 0.902299638

00:33:03.044 --> 00:33:04.756 of balance and coordination.

NOTE Confidence: 0.798463808888889

00:33:06.960 --> 00:33:08.870 Another change that she noticed

NOTE Confidence: 0.798463808888889

00:33:08.870 --> 00:33:11.438 is a grip strength of mice.

NOTE Confidence: 0.798463808888889

00:33:11.438 --> 00:33:14.033 Again, animals are allowed to

NOTE Confidence: 0.798463808888889

00:33:14.033 --> 00:33:17.616 hang on to this sort of a mesh

NOTE Confidence: 0.798463808888889

00:33:17.616 --> 00:33:19.860 and we're measuring the amount of

NOTE Confidence: 0.798463808888889

00:33:19.945 --> 00:33:21.896 grip strength that these animals

NOTE Confidence: 0.798463808888889

00:33:21.896 --> 00:33:24.080 have until they kind of fall off.

NOTE Confidence: 0.798463808888889

00:33:24.080 --> 00:33:26.282 And this indicated that auto antibodies

NOTE Confidence: 0.798463808888889

00:33:26.282 --> 00:33:28.131 can induce reduction in muscle

NOTE Confidence: 0.798463808888889

00:33:28.131 --> 00:33:30.336 strength because you can look at the

NOTE Confidence: 0.798463808888889

00:33:30.336 --> 00:33:32.184 peak force being quite diminished

NOTE Confidence: 0.798463808888889

00:33:32.184 --> 00:33:34.800 in those animals that received IgG.

NOTE Confidence: 0.837536818235294

00:33:36.960 --> 00:33:40.146 And thermal sensation using hot plate

NOTE Confidence: 0.837536818235294

00:33:40.146 --> 00:33:42.863 test also demonstrated that latency

NOTE Confidence: 0.837536818235294

00:33:42.863 --> 00:33:45.875 to pain behavior is much shortened,

NOTE Confidence: 0.837536818235294

00:33:45.880 --> 00:33:49.438 meaning that auto antibodies are sufficient

NOTE Confidence: 0.837536818235294

00:33:49.438 --> 00:33:53.000 to increase sensitivity to thermal pain.

NOTE Confidence: 0.837536818235294

00:33:53.000 --> 00:33:55.010 So these tests are now indicating

NOTE Confidence: 0.837536818235294

00:33:55.010 --> 00:33:57.234 to us that there's a physiological

NOTE Confidence: 0.837536818235294

00:33:57.234 --> 00:33:59.670 change that happened only by injecting

NOTE Confidence: 0.837536818235294

00:33:59.670 --> 00:34:02.039 IgG from patients into the mice.

NOTE Confidence: 0.837536818235294

00:34:02.040 --> 00:34:04.455 And it also implies that whatever auto

NOTE Confidence: 0.837536818235294

00:34:04.455 --> 00:34:06.685 antigens that are being detected are

NOTE Confidence: 0.837536818235294

00:34:06.685 --> 00:34:09.080 shared between these two two species.

NOTE Confidence: 0.9402185172

00:34:11.360 --> 00:34:13.803 And finally, I'd like to give you

NOTE Confidence: 0.9402185172

00:34:13.803 --> 00:34:16.162 a little example of tissue damage

NOTE Confidence: 0.9402185172

00:34:16.162 --> 00:34:18.222 and dysfunction that can happen

NOTE Confidence: 0.9402185172

00:34:18.222 --> 00:34:20.797 after even a very mild acute COVID.

NOTE Confidence: 0.9402185172

00:34:20.800 --> 00:34:24.036 This is a study that we had the fortune

NOTE Confidence: 0.9402185172

00:34:24.036 --> 00:34:26.370 of doing with Professor Michelle Monje's

NOTE Confidence: 0.9402185172

00:34:26.438 --> 00:34:29.452 group at Stanford where she's a a

NOTE Confidence: 0.9402185172

00:34:29.452 --> 00:34:32.290 neuroscientist and A and a psychiatrist

NOTE Confidence: 0.9402185172

00:34:32.382 --> 00:34:35.478 who have been studying the impact of

NOTE Confidence: 0.9402185172

00:34:35.480 --> 00:34:37.964 chemotherapy on brain dysfunction.

NOTE Confidence: 0.9402185172

00:34:37.964 --> 00:34:42.759 And based on her knowledge of this area,

NOTE Confidence: 0.9402185172

00:34:42.760 --> 00:34:47.384 we collaborated to look at the impact of

NOTE Confidence: 0.9402185172

00:34:47.384 --> 00:34:51.278 mild respiratory only infection on the CNS.

NOTE Confidence: 0.9402185172

00:34:51.280 --> 00:34:53.910 So a respiratory infection can

NOTE Confidence: 0.9402185172

00:34:53.910 --> 00:34:57.324 cause CNS impact by either directly

NOTE Confidence: 0.9402185172

00:34:57.324 --> 00:35:00.394 infecting brain cells or generating

NOTE Confidence: 0.9402185172

00:35:00.394 --> 00:35:02.879 autoimmunity that targets the brain.

NOTE Confidence: 0.9402185172

00:35:02.880 --> 00:35:05.300 Or it's possible that distal

NOTE Confidence: 0.9402185172

00:35:05.300 --> 00:35:07.720 inflammation alone is capable of

NOTE Confidence: 0.9402185172

00:35:07.720 --> 00:35:10.840 making chronic changes in the brain.

NOTE Confidence: 0.9402185172

00:35:10.840 --> 00:35:13.515 So this study really probes

NOTE Confidence: 0.9402185172

00:35:13.515 --> 00:35:15.120 the third hypothesis.

NOTE Confidence: 0.9402185172

00:35:15.120 --> 00:35:17.776 And the way in which we did this

NOTE Confidence: 0.9402185172

00:35:17.776 --> 00:35:20.075 is to we had an established animal

NOTE Confidence: 0.9402185172

00:35:20.075 --> 00:35:22.244 model in which we can introduce

NOTE Confidence: 0.9402185172

00:35:22.244 --> 00:35:24.080 the viral entry receptor,

NOTE Confidence: 0.9402185172

00:35:24.080 --> 00:35:27.600 human ACE 2 into any organ of choice.

NOTE Confidence: 0.9402185172

00:35:27.600 --> 00:35:29.536 Here we're doing intratracheal

NOTE Confidence: 0.9402185172

00:35:29.536 --> 00:35:31.956 administration so that the lung

NOTE Confidence: 0.9402185172

00:35:31.956 --> 00:35:34.698 is the only organ in which the

NOTE Confidence: 0.9402185172

00:35:34.698 --> 00:35:37.280 Tsarsco V2 can infect and replicate.

NOTE Confidence: 0.9402185172

00:35:37.280 --> 00:35:40.038 Then we give a Tsarsco V2 intranasally

NOTE Confidence: 0.9402185172

00:35:40.040 --> 00:35:41.600 after about a couple weeks.

NOTE Confidence: 0.9402185172

00:35:41.600 --> 00:35:44.512 And then we looked at the brain

NOTE Confidence: 0.9402185172

00:35:44.512 --> 00:35:46.432 sections here and of course there

NOTE Confidence: 0.9402185172

00:35:46.432 --> 00:35:48.000 is no entry receptor in the brain.

NOTE Confidence: 0.9402185172

00:35:48.000 --> 00:35:49.908 So we don't see any Tsarsco

NOTE Confidence: 0.9402185172

00:35:49.908 --> 00:35:51.680 V2 antigen in the brain.

NOTE Confidence: 0.9402185172

00:35:51.680 --> 00:35:53.678 Animals don't lose much weight either.

NOTE Confidence: 0.9402185172

00:35:53.680 --> 00:35:56.320 This is a very mild infection,

NOTE Confidence: 0.9402185172

00:35:56.320 --> 00:35:59.428 but we know that the viral antigen

NOTE Confidence: 0.9402185172

00:35:59.428 --> 00:36:01.678 is abundantly expressed in the lung

NOTE Confidence: 0.9402185172

00:36:01.680 --> 00:36:04.140 around 7:00 and which is cleared

NOTE Confidence: 0.9402185172

00:36:04.140 --> 00:36:06.960 within about seven days post infection.

NOTE Confidence: 0.9402185172

00:36:06.960 --> 00:36:09.435 So using this respiratory only

NOTE Confidence: 0.9402185172

00:36:09.435 --> 00:36:10.920 mild COVID model,

NOTE Confidence: 0.9402185172

00:36:10.920 --> 00:36:13.320 we then went on to look in the

NOTE Confidence: 0.9402185172

00:36:13.320 --> 00:36:16.080 cytokine in the serum and within

NOTE Confidence: 0.9402185172

00:36:16.080 --> 00:36:18.855 the cerebral spinal fluid of these

NOTE Confidence: 0.9402185172

00:36:18.855 --> 00:36:20.885 animals and at seven days post

NOTE Confidence: 0.9402185172

00:36:20.885 --> 00:36:22.943 infection on the left and seven

NOTE Confidence: 0.9402185172

00:36:22.943 --> 00:36:25.235 weeks post infection on the right.

NOTE Confidence: 0.9402185172

00:36:25.240 --> 00:36:28.456 And what we noted is that even at

NOTE Confidence: 0.9402185172

00:36:28.456 --> 00:36:31.172 7 weeks post infection you see a

NOTE Confidence: 0.9402185172

00:36:31.172 --> 00:36:33.767 still elevation of cytokines and

NOTE Confidence: 0.9402185172

00:36:33.767 --> 00:36:36.506 chemokines in the both the serum

NOTE Confidence: 0.9402185172

00:36:36.506 --> 00:36:38.034 and serial spinal fluid.

NOTE Confidence: 0.9402185172

00:36:38.040 --> 00:36:40.679 And one thing to know is the

NOTE Confidence: 0.9402185172

00:36:40.680 --> 00:36:44.680 OR elevated CCL 11 expression.

NOTE Confidence: 0.9402185172

00:36:44.680 --> 00:36:48.066 Now CCL 11 has been shown by others

NOTE Confidence: 0.9402185172

00:36:48.066 --> 00:36:51.252 in the past to correlate with

NOTE Confidence: 0.9402185172

00:36:51.252 --> 00:36:54.556 neurocognitive decline during aging.

NOTE Confidence: 0.9402185172

00:36:54.560 --> 00:36:56.288 And so we're seeing the elevated

NOTE Confidence: 0.9402185172

00:36:56.288 --> 00:36:57.440 levels of that here.

NOTE Confidence: 0.969636594545455

00:37:00.040 --> 00:37:02.788 And interestingly, when we look in

NOTE Confidence: 0.969636594545455

00:37:02.788 --> 00:37:05.571 the brain of these animals either

NOTE Confidence: 0.969636594545455

00:37:05.571 --> 00:37:07.579 seven days on on the top or seven

NOTE Confidence: 0.969636594545455

00:37:07.579 --> 00:37:09.478 weeks post infection on the bottom,

NOTE Confidence: 0.969636594545455

00:37:09.480 --> 00:37:12.648 we see a a consistently elevated

NOTE Confidence: 0.969636594545455

00:37:12.648 --> 00:37:15.170 reactive microglia in the subcortical

NOTE Confidence: 0.969636594545455

00:37:15.170 --> 00:37:18.040 white matter of two strains of animals.

NOTE Confidence: 0.969636594545455

00:37:18.040 --> 00:37:21.775 We tested CD1 and Bob C and you can

NOTE Confidence: 0.969636594545455

00:37:21.775 --> 00:37:23.400 see the micrograph showing here.

NOTE Confidence: 0.912753564285714

00:37:26.720 --> 00:37:30.234 We also validated or looked at humans.

NOTE Confidence: 0.912753564285714

00:37:30.240 --> 00:37:32.760 We validated in mice, we look at humans.

NOTE Confidence: 0.912753564285714

00:37:32.760 --> 00:37:34.920 We looked at humans who

NOTE Confidence: 0.912753564285714

00:37:34.920 --> 00:37:38.080 have had died with COVID.

NOTE Confidence: 0.912753564285714

00:37:38.080 --> 00:37:41.160 So these people had source COVID 2 PCR

NOTE Confidence: 0.912753564285714

00:37:41.160 --> 00:37:44.288 positive at the time of death but they

NOTE Confidence: 0.912753564285714

00:37:44.288 --> 00:37:46.708 weren't suffering from acute respiratory

NOTE Confidence: 0.912753564285714

00:37:46.708 --> 00:37:49.000 distress syndrome at that point.

NOTE Confidence: 0.912753564285714

00:37:49.000 --> 00:37:51.800 They they they died of some other causes.

NOTE Confidence: 0.912753564285714

00:37:51.800 --> 00:37:54.638 And even though that's the case,

NOTE Confidence: 0.912753564285714

00:37:54.640 --> 00:37:57.840 the mild COVID patients autopsy

NOTE Confidence: 0.912753564285714

00:37:57.840 --> 00:38:00.330 results show that there is increases

NOTE Confidence: 0.912753564285714

00:38:00.330 --> 00:38:03.078 in the reactive Mycoglia in the white

NOTE Confidence: 0.912753564285714

00:38:03.078 --> 00:38:05.118 matter of these these patients who

NOTE Confidence: 0.912753564285714

00:38:05.118 --> 00:38:07.837 or people who passed away with COVID.

NOTE Confidence: 0.916569013

00:38:10.240 --> 00:38:13.552 We also see an accompanying impairment

NOTE Confidence: 0.916569013

00:38:13.552 --> 00:38:16.520 of the hippocampal neurogenesis in seven

NOTE Confidence: 0.916569013

00:38:16.520 --> 00:38:18.800 days and seven weeks post infection.

NOTE Confidence: 0.916569013

00:38:18.800 --> 00:38:21.836 You can see that these neuroblasts

NOTE Confidence: 0.916569013

00:38:21.836 --> 00:38:24.392 are significantly reduced in those

NOTE Confidence: 0.916569013

00:38:24.392 --> 00:38:27.532 animals that had these mild COVID as

NOTE Confidence: 0.916569013

00:38:27.532 --> 00:38:30.696 well as elevated levels of CCL 11

00:38:30.696 --> 00:38:33.840 that I noted if a few slides ago.

00:38:33.840 --> 00:38:36.954 We see this not only in the mouse cerebral

00:38:36.954 --> 00:38:39.639 spinal fluid at 7 weeks post infection,

00:38:39.640 --> 00:38:42.200 but also in human serum.

00:38:42.200 --> 00:38:45.440 This was elevated in long COVID

00:38:45.440 --> 00:38:47.920 participants who who had brain fog,

00:38:50.880 --> 00:38:53.491 and we also examined some of the

00:38:53.491 --> 00:38:55.856 sort of downstream consequences of

00:38:55.856 --> 00:38:58.196 having these reactive microglia,

00:38:58.200 --> 00:39:01.300 which is expected to impact

00:39:01.300 --> 00:39:03.840 other glial cells and neurons.

00:39:03.840 --> 00:39:05.918 For instance, the oligodendrocytes

00:39:05.918 --> 00:39:09.272 in the corpus callosum of these

00:39:09.272 --> 00:39:11.599 animals were also reduced,

00:39:11.600 --> 00:39:15.992 as you can see at 7 weeks post infection.

NOTE Confidence: 0.868151046875

00:39:16.000 --> 00:39:19.624 And as a result of that we also

NOTE Confidence: 0.868151046875

00:39:19.624 --> 00:39:23.280 see loss of myelination of axons

NOTE Confidence: 0.868151046875

00:39:23.280 --> 00:39:26.896 within the cingulum of the corpus

NOTE Confidence: 0.868151046875

00:39:26.896 --> 00:39:29.445 callosum as indicated here at 7

NOTE Confidence: 0.868151046875

00:39:29.445 --> 00:39:32.320 weeks and seven days post infection.

NOTE Confidence: 0.868151046875

00:39:32.320 --> 00:39:36.520 So All in all this study that

NOTE Confidence: 0.868151046875

00:39:36.520 --> 00:39:38.820 combines mouse model and human

NOTE Confidence: 0.868151046875

00:39:38.820 --> 00:39:42.000 brain illustrated that even a mild

NOTE Confidence: 0.868151046875

00:39:42.000 --> 00:39:44.176 respiratory psoroscovito infection can

NOTE Confidence: 0.868151046875

00:39:44.176 --> 00:39:47.702 have lasting impact on the CNS both

NOTE Confidence: 0.868151046875

00:39:47.702 --> 00:39:50.280 within the subcortical white matter

NOTE Confidence: 0.868151046875

00:39:50.280 --> 00:39:52.956 as well as within the hippocampus.

NOTE Confidence: 0.868151046875

00:39:52.960 --> 00:39:55.152 And then specifically received

NOTE Confidence: 0.868151046875

00:39:55.152 --> 00:39:57.892 reactive mycoglia elevated in these

NOTE Confidence: 0.868151046875

00:39:57.892 --> 00:40:00.584 tissues accompanied by a reduction

NOTE Confidence: 0.868151046875

00:40:00.584 --> 00:40:03.800 in oligodendrocyte numbers as well as

NOTE Confidence: 0.868151046875

00:40:03.885 --> 00:40:07.960 myelination of axons and a reduction in

NOTE Confidence: 0.868151046875

00:40:07.960 --> 00:40:10.360 neurogenesis within the hippocampus.

NOTE Confidence: 0.868151046875

00:40:10.360 --> 00:40:13.036 So this illustrates that you know,

NOTE Confidence: 0.868151046875

00:40:13.040 --> 00:40:15.504 you don't have to have direct infection

NOTE Confidence: 0.868151046875

00:40:15.504 --> 00:40:17.628 or direct immune pathology in the

NOTE Confidence: 0.868151046875

00:40:17.628 --> 00:40:19.959 brain to have a chronic changes that

NOTE Confidence: 0.868151046875

00:40:20.030 --> 00:40:22.360 could result in cognitive impairment.

NOTE Confidence: 0.870354215909091

00:40:24.840 --> 00:40:26.368 So collectively our findings

NOTE Confidence: 0.870354215909091

00:40:26.368 --> 00:40:28.278 show that reactivation of latent

NOTE Confidence: 0.870354215909091

00:40:28.278 --> 00:40:30.307 viruses like ebb is happening in a

NOTE Confidence: 0.870354215909091

00:40:30.307 --> 00:40:32.039 subset of people with long COVID.

NOTE Confidence: 0.870354215909091

00:40:32.040 --> 00:40:34.728 We see elevation of auto antibodies

NOTE Confidence: 0.870354215909091

00:40:34.728 --> 00:40:37.022 that are functionally pathological in

NOTE Confidence: 0.870354215909091

00:40:37.022 --> 00:40:40.319 in the mouse model that we created.

NOTE Confidence: 0.870354215909091

00:40:40.320 --> 00:40:43.440 And we also see that hormonal

NOTE Confidence: 0.870354215909091

00:40:43.440 --> 00:40:45.520 dysregulation is happening both

NOTE Confidence: 0.870354215909091

00:40:45.606 --> 00:40:48.771 likely stemming from the hypothalamus

NOTE Confidence: 0.870354215909091

00:40:48.771 --> 00:40:51.388 pituitary axis as well as sex

NOTE Confidence: 0.870354215909091

00:40:51.388 --> 00:40:53.073 hormone differences that we see.

NOTE Confidence: 0.870354215909091

00:40:53.080 --> 00:40:55.020 And there's a significant difference

NOTE Confidence: 0.870354215909091

00:40:55.020 --> 00:40:57.872 in male and female with respect to

NOTE Confidence: 0.870354215909091

00:40:57.872 --> 00:40:59.977 the symptoms and organ involvement

NOTE Confidence: 0.870354215909091

00:40:59.977 --> 00:41:02.430 and immune features that are

NOTE Confidence: 0.870354215909091

00:41:02.430 --> 00:41:06.000 happening in people with long COVID.

NOTE Confidence: 0.870354215909091

00:41:06.000 --> 00:41:08.037 So what do we do about these?

NOTE Confidence: 0.870354215909091

00:41:08.040 --> 00:41:10.906 Well, we'd love to kind of bring

NOTE Confidence: 0.870354215909091

00:41:10.906 --> 00:41:13.236 this forward to something that's

NOTE Confidence: 0.870354215909091

00:41:13.236 --> 00:41:14.634 useful in patients.

NOTE Confidence: 0.870354215909091

00:41:14.640 --> 00:41:17.096 So now that we kind of see evidence

NOTE Confidence: 0.870354215909091

00:41:17.096 --> 00:41:19.558 for these four types of root causes,

NOTE Confidence: 0.870354215909091

00:41:19.560 --> 00:41:21.736 one thing that one can do is to

NOTE Confidence: 0.870354215909091

00:41:21.736 --> 00:41:24.182 do a randomized clinical trial

NOTE Confidence: 0.870354215909091

00:41:24.182 --> 00:41:26.718 coupled with biological analysis.

NOTE Confidence: 0.870354215909091

00:41:26.720 --> 00:41:28.904 So for example, autoimmunity,

NOTE Confidence: 0.870354215909091

00:41:28.904 --> 00:41:32.013 there are many very useful biologics

NOTE Confidence: 0.870354215909091

00:41:32.013 --> 00:41:33.878 and drugs that are currently

NOTE Confidence: 0.870354215909091

00:41:33.878 --> 00:41:36.280 being used to treat autoimmunity.

NOTE Confidence: 0.870354215909091

00:41:36.280 --> 00:41:39.040 And whether we can use those types of

NOTE Confidence: 0.870354215909091

00:41:39.040 --> 00:41:42.696 approved drugs for treatment of long COVID,

NOTE Confidence: 0.870354215909091

00:41:42.696 --> 00:41:44.636 it's something to be seen.

NOTE Confidence: 0.799211830909091

00:41:47.240 --> 00:41:49.152 As Wilton already mentioned,

NOTE Confidence: 0.799211830909091

00:41:49.152 --> 00:41:52.020 we are collaborating with Harlan Krumholz

NOTE Confidence: 0.799211830909091

00:41:52.098 --> 00:41:54.995 group to carry out this Yelpak Slovak trial.

NOTE Confidence: 0.799211830909091

00:41:55.000 --> 00:41:58.185 This is a decentralized trial in that

NOTE Confidence: 0.799211830909091

00:41:58.185 --> 00:42:02.200 anyone in the contiguous US can participate.

NOTE Confidence: 0.799211830909091

00:42:02.200 --> 00:42:05.000 It's an online recruitment.

NOTE Confidence: 0.799211830909091

00:42:05.000 --> 00:42:06.666 We send the drugs to the the

NOTE Confidence: 0.799211830909091

00:42:06.666 --> 00:42:08.200 homes of the participants.

NOTE Confidence: 0.799211830909091

00:42:08.200 --> 00:42:12.085 We send phlebotomist to collect blood and

NOTE Confidence: 0.799211830909091

00:42:12.085 --> 00:42:14.480 saliva before and after the treatment.

NOTE Confidence: 0.799211830909091

00:42:14.480 --> 00:42:17.700 And we are doing a deep symptom

NOTE Confidence: 0.799211830909091

00:42:17.700 --> 00:42:20.064 survey all kind of electronically.

NOTE Confidence: 0.799211830909091

00:42:20.064 --> 00:42:23.389 And this is a revolutionary thing that

NOTE Confidence: 0.799211830909091

00:42:23.389 --> 00:42:26.320 Harlan is doing with this trial and I'm

NOTE Confidence: 0.799211830909091

00:42:26.320 --> 00:42:29.158 really kind of excited to be part of it.

NOTE Confidence: 0.799211830909091

00:42:29.160 --> 00:42:32.508 We are contributing more of the

NOTE Confidence: 0.799211830909091

00:42:32.508 --> 00:42:34.740 biological analysis that accompanies

NOTE Confidence: 0.799211830909091

00:42:34.831 --> 00:42:37.422 this and I think that's very important

NOTE Confidence: 0.799211830909091

00:42:37.422 --> 00:42:39.900 because let's say Pakslovid improves

NOTE Confidence: 0.799211830909091

00:42:39.900 --> 00:42:43.440 the symptoms in 10% of the participants.

NOTE Confidence: 0.799211830909091

00:42:43.440 --> 00:42:47.154 We should be able to find biomarkers

NOTE Confidence: 0.799211830909091

00:42:47.154 --> 00:42:50.968 of success in those temptations that

NOTE Confidence: 0.799211830909091

00:42:50.968 --> 00:42:54.664 then would help others who have those

NOTE Confidence: 0.799211830909091

00:42:54.664 --> 00:42:57.768 biomarkers as potential sort of you know

NOTE Confidence: 0.799211830909091

00:42:57.768 --> 00:43:00.280 candidates for treatment with Pakslovid.

NOTE Confidence: 0.799211830909091

00:43:00.280 --> 00:43:02.905 And it also gives us an empirical

NOTE Confidence: 0.799211830909091

00:43:02.905 --> 00:43:05.085 biomarker for success with Paxlovid

NOTE Confidence: 0.799211830909091

00:43:05.085 --> 00:43:07.049 which really implies persistent

NOTE Confidence: 0.799211830909091

00:43:07.049 --> 00:43:09.826 virus replication as being the the

NOTE Confidence: 0.799211830909091

00:43:09.826 --> 00:43:11.676 root cause for those patients.

NOTE Confidence: 0.799211830909091

00:43:11.680 --> 00:43:14.101 So this is a 15 day oral Paxlovid trial

NOTE Confidence: 0.799211830909091

00:43:14.101 --> 00:43:16.526 which is much longer than the five day

NOTE Confidence: 0.799211830909091

00:43:16.526 --> 00:43:19.039 course that we're using for the acute phase.

NOTE Confidence: 0.799211830909091

00:43:19.040 --> 00:43:21.672 We think it's 15 days are necessary

NOTE Confidence: 0.799211830909091

00:43:21.672 --> 00:43:23.680 because of the slowly replicating

NOTE Confidence: 0.799211830909091

00:43:23.680 --> 00:43:25.880 nature of these persistent reservoir.

NOTE Confidence: 0.880226869230769

00:43:28.040 --> 00:43:30.574 We're also very excited to have another

NOTE Confidence: 0.880226869230769

00:43:30.574 --> 00:43:32.960 trial ongoing which we're just starting.

NOTE Confidence: 0.880226869230769

00:43:32.960 --> 00:43:36.476 Actually Doctor was Eli from Vanderbilt

NOTE Confidence: 0.880226869230769

00:43:36.480 --> 00:43:39.210 is leading this anti-inflammatory agent

NOTE Confidence: 0.880226869230769

00:43:39.210 --> 00:43:42.720 study well Jack inhibitor this is called

NOTE Confidence: 0.880226869230769

00:43:42.720 --> 00:43:45.476 reverse LC trial which we are beginning

NOTE Confidence: 0.880226869230769

00:43:45.476 --> 00:43:48.990 soon and again we will be contributing some

NOTE Confidence: 0.880226869230769

00:43:48.990 --> 00:43:52.195 immunological analysis and insights there.

NOTE Confidence: 0.880226869230769

00:43:52.200 --> 00:43:55.740 And finally with David Petrino we're

NOTE Confidence: 0.880226869230769

00:43:55.740 --> 00:43:58.100 doing antiviral randomized clinical

NOTE Confidence: 0.880226869230769

00:43:58.187 --> 00:44:00.730 trial targeting latent EBB reactivation.

NOTE Confidence: 0.880226869230769

00:44:00.730 --> 00:44:04.420 So I think you know knowing some of these

NOTE Confidence: 0.880226869230769

00:44:04.498 --> 00:44:07.312 key features are really helping us to

NOTE Confidence: 0.880226869230769

00:44:07.312 --> 00:44:10.325 target the right kinds of pathways with

NOTE Confidence: 0.880226869230769

00:44:10.325 --> 00:44:13.674 an already approved drug that can we we

NOTE Confidence: 0.880226869230769

00:44:13.674 --> 00:44:17.080 are hoping to help patients with on COVID.

NOTE Confidence: 0.880226869230769

00:44:17.080 --> 00:44:19.760 So the mystery is there,

00:44:19.760 --> 00:44:22.091 but it's being solved and we are

00:44:22.091 --> 00:44:24.120 scratching the surface of this mystery,

00:44:24.120 --> 00:44:26.100 but at least we're seeing

00:44:26.100 --> 00:44:28.080 something underneath this the the,

00:44:28.080 --> 00:44:31.120 the thin layer that we are scratching and

00:44:31.120 --> 00:44:34.546 very excited to be able to progress in this

00:44:34.546 --> 00:44:38.038 both for the diagnosis and therapeutics

00:44:38.040 --> 00:44:39.756 and looking further into the future,

00:44:39.760 --> 00:44:41.951 of course we want to prevent these

00:44:41.951 --> 00:44:44.842 diseases from ever happening and we are

00:44:44.842 --> 00:44:46.658 pursuing mucosal vaccine strategies

00:44:46.658 --> 00:44:49.683 that would enable people not only to

00:44:49.683 --> 00:44:52.065 be preventing severe disease but also

00:44:52.142 --> 00:44:54.838 infection and transmission altogether,

00:44:54.840 --> 00:44:57.840 which would by definition prevent

NOTE Confidence: 0.880226869230769

00:44:57.840 --> 00:45:00.240 post acute infection syndromes.

NOTE Confidence: 0.880226869230769

00:45:00.240 --> 00:45:02.430 And we're also looking at therapies

NOTE Confidence: 0.880226869230769

00:45:02.430 --> 00:45:04.790 for post acute infection syndromes that

NOTE Confidence: 0.880226869230769

00:45:04.790 --> 00:45:07.336 hopefully will inform things like MECFS.

NOTE Confidence: 0.880226869230769

00:45:07.336 --> 00:45:11.440 Once we identify the root causes in one pies,

NOTE Confidence: 0.880226869230769

00:45:11.440 --> 00:45:13.992 we know we should be able to apply

NOTE Confidence: 0.880226869230769

00:45:13.992 --> 00:45:16.198 the same strategy for others.

NOTE Confidence: 0.880226869230769

00:45:16.200 --> 00:45:18.797 So I want to acknowledge the the,

NOTE Confidence: 0.880226869230769

00:45:18.800 --> 00:45:20.492 the amazing team that I have

NOTE Confidence: 0.880226869230769

00:45:20.492 --> 00:45:21.960 the fortune of working with.

NOTE Confidence: 0.880226869230769

00:45:21.960 --> 00:45:23.388 I have only was able to tell

NOTE Confidence: 0.880226869230769

00:45:23.388 --> 00:45:24.600 you a couple of stories,

NOTE Confidence: 0.880226869230769

00:45:24.600 --> 00:45:26.502 but they're just like amazing things

NOTE Confidence: 0.880226869230769

00:45:26.502 --> 00:45:29.234 going on right now and the very generous

NOTE Confidence: 0.880226869230769

00:45:29.234 --> 00:45:31.719 funders that support our research.

NOTE Confidence: 0.880226869230769

00:45:31.720 --> 00:45:32.332 And finally,

NOTE Confidence: 0.880226869230769

00:45:32.332 --> 00:45:34.474 just a special thank you to all

NOTE Confidence: 0.880226869230769

00:45:34.474 --> 00:45:36.535 the participants and the patients

NOTE Confidence: 0.880226869230769

00:45:36.535 --> 00:45:37.746 who provided efforts,

NOTE Confidence: 0.880226869230769

00:45:37.746 --> 00:45:40.104 time and their specimen in order

NOTE Confidence: 0.880226869230769

00:45:40.104 --> 00:45:42.198 for us to learn together.

NOTE Confidence: 0.880226869230769

00:45:42.200 --> 00:45:44.520 So thank you so much for your attention.

NOTE Confidence: 0.709623501428571

00:45:48.680 --> 00:45:50.276 Some thank you so much Doctor Rasaki,

NOTE Confidence: 0.709623501428571

00:45:50.280 --> 00:45:52.786 that was a great presentation for those

NOTE Confidence: 0.709623501428571

00:45:52.786 --> 00:45:55.055 of us who are still in the on the call.

NOTE Confidence: 0.709623501428571

00:45:55.055 --> 00:45:55.880 If you have a question,

NOTE Confidence: 0.709623501428571

00:45:55.880 --> 00:45:57.518 you can use the Q&amp;A function,

NOTE Confidence: 0.709623501428571

00:45:57.520 --> 00:45:59.823 you can just type in your question

NOTE Confidence: 0.709623501428571

00:45:59.823 --> 00:46:01.958 and then we'll relay them over.

NOTE Confidence: 0.709623501428571

00:46:01.960 --> 00:46:03.358 But again, thank you so much.

NOTE Confidence: 0.709623501428571

00:46:03.360 --> 00:46:06.458 I just had a quick question, you know,

NOTE Confidence: 0.709623501428571

00:46:06.458 --> 00:46:08.072 especially regarding you know some of

NOTE Confidence: 0.709623501428571

00:46:08.072 --> 00:46:09.917 the data you showed about you know,

NOTE Confidence: 0.709623501428571

00:46:09.920 --> 00:46:11.858 lower levels of cortisol and like

NOTE Confidence: 0.709623501428571

00:46:11.858 --> 00:46:13.743 testosterone or estradiol and some of

NOTE Confidence: 0.709623501428571

00:46:13.743 --> 00:46:15.357 those patients who had long COVID.

NOTE Confidence: 0.709623501428571

00:46:15.360 --> 00:46:17.628 I think given since long COVID has

NOTE Confidence: 0.709623501428571

00:46:17.628 --> 00:46:19.614 all these different symptoms and it's

NOTE Confidence: 0.709623501428571

00:46:19.614 --> 00:46:21.840 really hard to sort of diagnose and

NOTE Confidence: 0.709623501428571

00:46:21.840 --> 00:46:24.104 and sort of sort of spot like how

NOTE Confidence: 0.709623501428571

00:46:24.104 --> 00:46:26.186 feasible would it be to use those sorts

NOTE Confidence: 0.709623501428571

00:46:26.186 --> 00:46:28.445 of levels to as like a screening tour

NOTE Confidence: 0.709623501428571

00:46:28.445 --> 00:46:30.735 or like a bio marker that people could

NOTE Confidence: 0.709623501428571

00:46:30.735 --> 00:46:32.552 clinically use to sort of indicate, hey,

NOTE Confidence: 0.709623501428571

00:46:32.552 --> 00:46:34.360 maybe this person does have long COVID.

NOTE Confidence: 0.709623501428571

00:46:34.360 --> 00:46:36.232 So just wanted to kind of hear

NOTE Confidence: 0.709623501428571

00:46:36.232 --> 00:46:37.000 your thoughts on that.

NOTE Confidence: 0.845074187142857

00:46:37.600 --> 00:46:40.519 Yeah. So in in our own cohort,

NOTE Confidence: 0.845074187142857

00:46:40.520 --> 00:46:44.168 those handful of markers were sufficient

NOTE Confidence: 0.845074187142857

00:46:44.168 --> 00:46:46.890 to very accurately diagnose long

NOTE Confidence: 0.845074187142857

00:46:46.890 --> 00:46:49.115 COVID using the machine learning.

NOTE Confidence: 0.845074187142857

00:46:49.120 --> 00:46:52.400 So I I think we can get there.

NOTE Confidence: 0.845074187142857

00:46:52.400 --> 00:46:54.570 It's just that because every

NOTE Confidence: 0.845074187142857

00:46:54.570 --> 00:46:56.306 physician diagnosed this long

NOTE Confidence: 0.845074187142857

00:46:56.306 --> 00:46:58.240 COVID slightly differently.

NOTE Confidence: 0.845074187142857

00:46:58.240 --> 00:47:00.172 So that that's really kind of the

NOTE Confidence: 0.845074187142857

00:47:00.172 --> 00:47:03.100 problem is that because the diagnostic

NOTE Confidence: 0.845074187142857

00:47:03.100 --> 00:47:06.600 criteria used are not uniform,

NOTE Confidence: 0.845074187142857

00:47:06.600 --> 00:47:10.778 you know we may not be able to use one type

NOTE Confidence: 0.845074187142857

00:47:10.778 --> 00:47:14.320 of biomarkers to as a diagnostic tool.

NOTE Confidence: 0.845074187142857

00:47:14.320 --> 00:47:17.200 So the Mount Sinai clinic where

NOTE Confidence: 0.845074187142857

00:47:17.200 --> 00:47:19.252 these patients were recruited from,

NOTE Confidence: 0.845074187142857

00:47:19.252 --> 00:47:21.072 they have pretty strict guidelines

NOTE Confidence: 0.845074187142857

00:47:21.072 --> 00:47:23.476 as to how they define long COVID.

NOTE Confidence: 0.845074187142857

00:47:23.480 --> 00:47:24.992 And I think that's helping us

NOTE Confidence: 0.845074187142857

00:47:24.992 --> 00:47:26.480 come up with these markers.

NOTE Confidence: 0.845074187142857

00:47:26.480 --> 00:47:27.209 But so yeah,

NOTE Confidence: 0.845074187142857

00:47:27.209 --> 00:47:29.480 it's kind of a chicken and egg question,

NOTE Confidence: 0.845074187142857

00:47:29.480 --> 00:47:32.155 right, 'cause if you're not

NOTE Confidence: 0.845074187142857

00:47:32.155 --> 00:47:33.760 diagnosing them properly,

NOTE Confidence: 0.845074187142857

00:47:33.760 --> 00:47:37.280 those patients cannot be used as a sort

NOTE Confidence: 0.845074187142857

00:47:37.280 --> 00:47:40.320 of platform to generate a biomarker.

NOTE Confidence: 0.845074187142857

00:47:40.320 --> 00:47:43.752 And so it's kind of a problem both ways,

NOTE Confidence: 0.845074187142857

00:47:43.752 --> 00:47:46.320 but we are hoping to be able to,

NOTE Confidence: 0.845074187142857

00:47:46.320 --> 00:47:47.056 for instance,

NOTE Confidence: 0.845074187142857

00:47:47.056 --> 00:47:49.632 let's say if these four drivers are,

NOTE Confidence: 0.845074187142857

00:47:49.640 --> 00:47:52.080 you know, creating the disease,

NOTE Confidence: 0.845074187142857

00:47:52.080 --> 00:47:54.075 we should be able to get biomarkers

NOTE Confidence: 0.845074187142857

00:47:54.075 --> 00:47:55.360 for each of these.

NOTE Confidence: 0.845074187142857

00:47:55.360 --> 00:47:57.064 I mean there's some of them are pretty

NOTE Confidence: 0.845074187142857

00:47:57.064 --> 00:47:58.320 simple, right, Like if it's SARS,

NOTE Confidence: 0.845074187142857

00:47:58.320 --> 00:47:59.816 COVID 2 that's persistent,

NOTE Confidence: 0.845074187142857

00:47:59.816 --> 00:48:02.060 we should be able to just

NOTE Confidence: 0.845074187142857

00:48:02.142 --> 00:48:03.798 measure their you know,

NOTE Confidence: 0.845074187142857

00:48:03.800 --> 00:48:05.775 viral antigens and circulations or

NOTE Confidence: 0.845074187142857

00:48:05.775 --> 00:48:08.184 something like this which some people

NOTE Confidence: 0.845074187142857

00:48:08.184 --> 00:48:09.558 are doing already autoimmunity.

NOTE Confidence: 0.845074187142857

00:48:09.558 --> 00:48:12.060 You know if we had a panel of auto

NOTE Confidence: 0.845074187142857

00:48:12.125 --> 00:48:14.274 antibody we can order right from Quest

NOTE Confidence: 0.845074187142857

00:48:14.274 --> 00:48:16.477 that that that should also cover it.

NOTE Confidence: 0.845074187142857

00:48:16.480 --> 00:48:20.224 So I think if we can identify more the

NOTE Confidence: 0.845074187142857

00:48:20.224 --> 00:48:23.594 molecular sort of agents that we can target,

NOTE Confidence: 0.845074187142857

00:48:23.600 --> 00:48:25.245 we're hoping to to be able to

NOTE Confidence: 0.845074187142857

00:48:25.245 --> 00:48:27.080 do that as a diagnostic tool.

NOTE Confidence: 0.90091896

00:48:29.240 --> 00:48:30.160 Awesome. Thank you so much.

NOTE Confidence: 0.90091896

00:48:30.160 --> 00:48:32.645 It looks like we do have one

NOTE Confidence: 0.90091896

00:48:32.645 --> 00:48:34.605 question as you know from someone

NOTE Confidence: 0.90091896

00:48:34.605 --> 00:48:36.671 related to my question was would

NOTE Confidence: 0.90091896

00:48:36.671 --> 00:48:38.626 you consider the clinical syndrome

NOTE Confidence: 0.90091896

00:48:38.626 --> 00:48:41.261 of adrenal fatigue to be some sort

NOTE Confidence: 0.90091896

00:48:41.261 --> 00:48:43.277 of a post acute infection syndrome?

NOTE Confidence: 0.883779592857143

00:48:44.240 --> 00:48:45.443 Yeah, great question.

NOTE Confidence: 0.883779592857143

00:48:45.443 --> 00:48:47.448 So adrenal fatigue is something

NOTE Confidence: 0.883779592857143

00:48:47.448 --> 00:48:49.960 that we are really interested in.

NOTE Confidence: 0.883779592857143

00:48:49.960 --> 00:48:52.056 I mean that was a basically the the

NOTE Confidence: 0.883779592857143

00:48:52.056 --> 00:48:54.822 biggest thing that hit us in the in

NOTE Confidence: 0.883779592857143

00:48:54.822 --> 00:48:56.634 the face right with this analysis.

NOTE Confidence: 0.883779592857143

00:48:56.640 --> 00:49:00.942 So right now what we are doing is we

NOTE Confidence: 0.883779592857143

00:49:00.942 --> 00:49:03.768 collected A saliva from long COVID

00:49:03.768 --> 00:49:06.876 patients over the 48 hours time window.

00:49:06.880 --> 00:49:09.806 There are 12 collections and and we're

00:49:09.806 --> 00:49:13.217 doing a very kind of detailed high

00:49:13.217 --> 00:49:16.319 resolution mapping of the cortisol level,

00:49:16.320 --> 00:49:17.916 you know over that time period.

00:49:17.920 --> 00:49:19.720 And so we should be able to tell,

00:49:19.720 --> 00:49:22.800 you know, is it like a general, you know,

00:49:22.800 --> 00:49:25.320 adrenal fatigue and insufficiency or is

00:49:25.320 --> 00:49:28.358 there some sort of circadian, you know,

00:49:28.358 --> 00:49:31.634 this regulation that's leading to this?

00:49:31.640 --> 00:49:33.884 I think there's circadian rhythm is

00:49:33.884 --> 00:49:35.880 quite disrupted in these people.

00:49:35.880 --> 00:49:38.984 We know that from not only survey but

00:49:38.984 --> 00:49:40.960 also from other people's analysis.

00:49:40.960 --> 00:49:42.960 Jim Heath for example published

NOTE Confidence: 0.883779592857143

00:49:42.960 --> 00:49:44.000 this early on.

NOTE Confidence: 0.883779592857143

00:49:44.000 --> 00:49:46.674 So it could be many things happening.

NOTE Confidence: 0.883779592857143

00:49:46.680 --> 00:49:47.214 But yeah,

NOTE Confidence: 0.883779592857143

00:49:47.214 --> 00:49:49.083 that that that's a really key thing

NOTE Confidence: 0.883779592857143

00:49:49.083 --> 00:49:51.196 to nail down and and we're excited.

NOTE Confidence: 0.883779592857143

00:49:51.200 --> 00:49:53.720 We just shipped the saliva samples yesterday.

NOTE Confidence: 0.883779592857143

00:49:53.720 --> 00:49:54.160 So very,

NOTE Confidence: 0.675860816666667

00:49:56.000 --> 00:49:58.040 very exciting. It really is very,

NOTE Confidence: 0.675860816666667

00:49:58.040 --> 00:50:02.880 you know, hot off, depressed, awesome.

NOTE Confidence: 0.675860816666667

00:50:02.880 --> 00:50:04.722 Next question, are there any lessons

NOTE Confidence: 0.675860816666667

00:50:04.722 --> 00:50:06.609 learned from long COVID that could

NOTE Confidence: 0.675860816666667

00:50:06.609 --> 00:50:08.421 inform will be relevant to other

NOTE Confidence: 0.675860816666667

00:50:08.421 --> 00:50:10.360 conditions like chronic fatigue syndrome?

NOTE Confidence: 0.965063692

00:50:11.400 --> 00:50:13.176 I really hope so.

NOTE Confidence: 0.965063692

00:50:13.176 --> 00:50:15.840 That's why we are now including

NOTE Confidence: 0.965063692

00:50:15.840 --> 00:50:19.025 MECFS patients as a as a separate

NOTE Confidence: 0.965063692

00:50:19.025 --> 00:50:23.170 cohort as well as you know chronic

NOTE Confidence: 0.965063692

00:50:23.170 --> 00:50:26.532 Lyme patients because you know as

NOTE Confidence: 0.965063692

00:50:26.532 --> 00:50:29.197 I mentioned these Pais syndromes,

NOTE Confidence: 0.965063692

00:50:29.200 --> 00:50:32.946 they are not unique to COVID and the

NOTE Confidence: 0.965063692

00:50:32.946 --> 00:50:35.557 more we can understand the overlap and

NOTE Confidence: 0.965063692

00:50:35.557 --> 00:50:37.478 distinction between these diseases,

NOTE Confidence: 0.965063692

00:50:37.480 --> 00:50:39.352 the more we can sort of

NOTE Confidence: 0.965063692

00:50:39.352 --> 00:50:40.600 learn from each other.

NOTE Confidence: 0.965063692

00:50:40.600 --> 00:50:42.700 And so for instance it let's say

NOTE Confidence: 0.965063692

00:50:42.700 --> 00:50:44.997 you know a third of the people

NOTE Confidence: 0.965063692

00:50:45.000 --> 00:50:47.190 reactivated EBV and that's sort

NOTE Confidence: 0.965063692

00:50:47.190 --> 00:50:50.200 of causing some of the symptoms.

NOTE Confidence: 0.965063692

00:50:50.200 --> 00:50:53.266 I would expect similar kinds of

NOTE Confidence: 0.965063692

00:50:53.266 --> 00:50:55.839 impact in other conditions like

NOTE Confidence: 0.965063692

00:50:55.839 --> 00:51:00.824 MECFS and if if a drug works in EBV

NOTE Confidence: 0.965063692

00:51:00.824 --> 00:51:03.559 long COVID patients that should

NOTE Confidence: 0.965063692

00:51:03.559 --> 00:51:05.928 also work in EBVME patients.

NOTE Confidence: 0.965063692

00:51:05.928 --> 00:51:07.080 So, you know,

NOTE Confidence: 0.965063692

00:51:07.080 --> 00:51:09.187 we're hoping that these are going to

NOTE Confidence: 0.965063692

00:51:09.187 --> 00:51:10.839 be cross fertilizing and you know,

NOTE Confidence: 0.965063692

00:51:10.840 --> 00:51:14.277 able to come up with proper treatment

NOTE Confidence: 0.965063692

00:51:14.280 --> 00:51:16.284 that that's another thing that really

NOTE Confidence: 0.965063692

00:51:16.284 --> 00:51:18.563 drives me and others in the lab

NOTE Confidence: 0.965063692

00:51:18.563 --> 00:51:20.033 is the suffering that's happening

NOTE Confidence: 0.965063692

00:51:20.033 --> 00:51:22.119 and in people with ME it's just,

NOTE Confidence: 0.965063692

00:51:22.120 --> 00:51:23.684 it's just it's devastating.

NOTE Confidence: 0.965063692

00:51:23.684 --> 00:51:25.639 People are taking their lives.

NOTE Confidence: 0.965063692

00:51:25.640 --> 00:51:29.106 So this is an urgent and really

NOTE Confidence: 0.965063692

00:51:29.106 --> 00:51:31.638 severely unmet medical need.

NOTE Confidence: 0.760564076842105

00:51:33.800 --> 00:51:34.996 Yeah. Next question asks,

NOTE Confidence: 0.760564076842105

00:51:34.996 --> 00:51:36.790 do you know how diverse the

NOTE Confidence: 0.760564076842105

00:51:36.847 --> 00:51:38.662 four factors that you mentioned

NOTE Confidence: 0.760564076842105

00:51:38.662 --> 00:51:40.114 are with persistent virus,

NOTE Confidence: 0.760564076842105

00:51:40.120 --> 00:51:41.788 auto antibodies, reactivation and

NOTE Confidence: 0.760564076842105

00:51:41.788 --> 00:51:43.873 the dysregulation of the hormones?

NOTE Confidence: 0.760564076842105

00:51:43.880 --> 00:51:46.000 And what do you think is sort of

NOTE Confidence: 0.760564076842105

00:51:46.000 --> 00:51:47.863 the relationship with a chain of

NOTE Confidence: 0.760564076842105

00:51:47.863 --> 00:51:49.458 causality between being being between

NOTE Confidence: 0.760564076842105

00:51:49.458 --> 00:51:51.400 those four different factors? Yeah,

NOTE Confidence: 0.932585442307692

00:51:52.000 --> 00:51:54.884 great question. I wish I had a

NOTE Confidence: 0.932585442307692

00:51:54.884 --> 00:51:57.000 longitudinal sampling of all these

NOTE Confidence: 0.932585442307692

00:51:57.000 --> 00:51:59.675 people so I can see like what actually

NOTE Confidence: 0.932585442307692

00:51:59.675 --> 00:52:01.519 happened over the time course.

NOTE Confidence: 0.932585442307692

00:52:01.520 --> 00:52:05.060 But my thinking is that it

NOTE Confidence: 0.932585442307692

00:52:05.060 --> 00:52:07.480 all starts with SARS Co V2.

NOTE Confidence: 0.932585442307692

00:52:07.480 --> 00:52:09.620 Of course that infection,

NOTE Confidence: 0.932585442307692

00:52:09.620 --> 00:52:12.295 if it's not being properly

NOTE Confidence: 0.932585442307692

00:52:12.295 --> 00:52:13.999 managed in the body,

NOTE Confidence: 0.932585442307692

00:52:14.000 --> 00:52:17.556 the the virus can seed other organs,

NOTE Confidence: 0.932585442307692

00:52:17.560 --> 00:52:19.576 things like small intestine or large

NOTE Confidence: 0.932585442307692

00:52:19.576 --> 00:52:21.321 intestine where people are finding

NOTE Confidence: 0.932585442307692

00:52:21.321 --> 00:52:23.373 viral antigens or in the meninges

NOTE Confidence: 0.932585442307692

00:52:23.373 --> 00:52:25.040 there's spike proteins everywhere.

NOTE Confidence: 0.932585442307692

00:52:25.040 --> 00:52:26.012 So you know,

NOTE Confidence: 0.932585442307692

00:52:26.012 --> 00:52:28.280 these types of events can happen if

NOTE Confidence: 0.932585442307692

00:52:28.355 --> 00:52:31.015 you don't control it at the respiratory

NOTE Confidence: 0.932585442307692

00:52:31.015 --> 00:52:33.520 tract and that can certainly trigger,

NOTE Confidence: 0.932585442307692

00:52:33.520 --> 00:52:34.800 you know,

NOTE Confidence: 0.932585442307692

00:52:34.800 --> 00:52:37.360 tissue dysfunction easily imaginable

NOTE Confidence: 0.932585442307692

00:52:37.360 --> 00:52:40.354 that can also trigger activation of

NOTE Confidence: 0.932585442307692

00:52:40.354 --> 00:52:43.382 bystander immune cells that can start

NOTE Confidence: 0.932585442307692

00:52:43.382 --> 00:52:45.757 to create these auto antibodies.

NOTE Confidence: 0.932585442307692

00:52:45.760 --> 00:52:48.448 And of course these old antibodies then

NOTE Confidence: 0.932585442307692

00:52:48.448 --> 00:52:50.879 can target things like hypothalamus,

NOTE Confidence: 0.932585442307692

00:52:50.880 --> 00:52:52.040 brain stem,

NOTE Confidence: 0.932585442307692

00:52:52.040 --> 00:52:54.940 whatever that then trigger these

NOTE Confidence: 0.932585442307692

00:52:54.940 --> 00:52:56.170 adrenal insufficiency, right.

NOTE Confidence: 0.932585442307692

00:52:56.170 --> 00:52:58.445 So I mean there are lots of

NOTE Confidence: 0.932585442307692

00:52:58.445 --> 00:52:59.878 arrows that one can draw,

NOTE Confidence: 0.932585442307692

00:52:59.880 --> 00:53:01.092 but that's sort of the way

NOTE Confidence: 0.932585442307692

00:53:01.092 --> 00:53:02.320 we're kind of thinking about it.

NOTE Confidence: 0.932585442307692

00:53:02.320 --> 00:53:03.928 It's just starting with the virus

NOTE Confidence: 0.932585442307692

00:53:03.928 --> 00:53:05.382 and all these other triggers

NOTE Confidence: 0.932585442307692

00:53:05.382 --> 00:53:06.678 that come come forward.

NOTE Confidence: 0.6358081

00:53:09.040 --> 00:53:11.622 Awesome. And then a follow up question

NOTE Confidence: 0.6358081

00:53:11.622 --> 00:53:13.078 for the very first question was there,

NOTE Confidence: 0.6358081

00:53:13.080 --> 00:53:15.042 are there any connections to long

NOTE Confidence: 0.6358081

00:53:15.042 --> 00:53:16.759 bacterial infections as well like

NOTE Confidence: 0.6358081

00:53:16.759 --> 00:53:18.519 the controversial like chronic Lyme

NOTE Confidence: 0.789592139090909

00:53:19.960 --> 00:53:21.163 syndrome. Yeah, exactly.

NOTE Confidence: 0.789592139090909

00:53:21.163 --> 00:53:24.400 So that that is why we're using this,

NOTE Confidence: 0.789592139090909

00:53:24.400 --> 00:53:26.775 we're we're kind of recruiting

NOTE Confidence: 0.789592139090909

00:53:26.775 --> 00:53:28.675 people with chronic Lyme.

NOTE Confidence: 0.789592139090909

00:53:28.680 --> 00:53:31.688 It is controversial unfortunately,

NOTE Confidence: 0.789592139090909

00:53:31.688 --> 00:53:34.944 but I I think we can sort of weed

NOTE Confidence: 0.789592139090909

00:53:34.944 --> 00:53:37.497 out some of the controversy by

NOTE Confidence: 0.789592139090909

00:53:37.497 --> 00:53:40.560 really focusing on the science,

NOTE Confidence: 0.789592139090909

00:53:40.560 --> 00:53:42.332 you know, science alone.

NOTE Confidence: 0.789592139090909

00:53:42.332 --> 00:53:45.416 Like it's just ensuring that what they

NOTE Confidence: 0.789592139090909

00:53:45.416 --> 00:53:48.720 have is explainable by biological factors.

NOTE Confidence: 0.789592139090909

00:53:48.720 --> 00:53:50.760 And if those factors are overlapping,

NOTE Confidence: 0.789592139090909

00:53:50.760 --> 00:53:52.212 say with long COVID,

NOTE Confidence: 0.789592139090909

00:53:52.212 --> 00:53:55.451 that will bring some sort of insights and

NOTE Confidence: 0.789592139090909

00:53:55.451 --> 00:53:58.397 legitimacy to these kinds of conditions.

NOTE Confidence: 0.789592139090909

00:53:58.400 --> 00:54:00.386 So, you know,

NOTE Confidence: 0.789592139090909

00:54:00.386 --> 00:54:01.638 we're completely open minded.

NOTE Confidence: 0.789592139090909

00:54:01.640 --> 00:54:03.482 We're just want to know what's

NOTE Confidence: 0.789592139090909

00:54:03.482 --> 00:54:05.559 going on and science will tell us,

NOTE Confidence: 0.789592139090909

00:54:05.560 --> 00:54:07.096 you know what way we need

NOTE Confidence: 0.789592139090909

00:54:07.096 --> 00:54:08.120 to interpret things but

NOTE Confidence: 0.856728809

00:54:09.400 --> 00:54:10.092 right. Awesome.

NOTE Confidence: 0.856728809

00:54:10.092 --> 00:54:12.168 The next question wanted you to

NOTE Confidence: 0.856728809

00:54:12.168 --> 00:54:14.822 ask if you could sort of elaborate

NOTE Confidence: 0.856728809

00:54:14.822 --> 00:54:16.712 regarding the the sex hormones,

NOTE Confidence: 0.856728809

00:54:16.720 --> 00:54:17.884 testosterone and and estrogen

NOTE Confidence: 0.856728809

00:54:17.884 --> 00:54:19.630 and do you think these are

NOTE Confidence: 0.856728809

00:54:19.682 --> 00:54:21.237 correlated or are they causative

NOTE Confidence: 0.856728809

00:54:21.237 --> 00:54:22.792 of the long COVID syndrome?

NOTE Confidence: 0.862175963333333

00:54:24.040 --> 00:54:26.665 Yeah. So there's a huge amount of

NOTE Confidence: 0.862175963333333

00:54:26.665 --> 00:54:28.800 correlation that I said already.

NOTE Confidence: 0.862175963333333

00:54:28.800 --> 00:54:30.888 The lower levels of testosterone really

NOTE Confidence: 0.862175963333333

00:54:30.888 --> 00:54:35.650 seems to be a a, a bad, you know,

NOTE Confidence: 0.862175963333333

00:54:35.650 --> 00:54:37.270 prognostic factor for developing

NOTE Confidence: 0.862175963333333

00:54:37.270 --> 00:54:40.124 all kinds of symptoms and and and

NOTE Confidence: 0.862175963333333

00:54:40.124 --> 00:54:41.680 other other immune pathologies.

NOTE Confidence: 0.862175963333333

00:54:41.680 --> 00:54:45.760 So testosterone has long been known

NOTE Confidence: 0.862175963333333

00:54:45.760 --> 00:54:47.960 to be have a immunosuppressive

NOTE Confidence: 0.862175963333333

00:54:48.035 --> 00:54:50.233 impact and it's also thought to be

NOTE Confidence: 0.862175963333333

00:54:50.233 --> 00:54:53.000 one of the reasons why women develop

NOTE Confidence: 0.862175963333333

00:54:53.000 --> 00:54:56.400 autoimmunity more often than men.

NOTE Confidence: 0.862175963333333

00:54:56.400 --> 00:54:58.710 And actually this whole thing started

NOTE Confidence: 0.862175963333333

00:54:58.710 --> 00:55:02.329 with a a parent of a a a trans child

NOTE Confidence: 0.862175963333333

00:55:02.329 --> 00:55:04.733 contacting me and telling me that the

NOTE Confidence: 0.862175963333333

00:55:04.733 --> 00:55:07.650 this child who has long COVID when they

NOTE Confidence: 0.862175963333333

00:55:07.650 --> 00:55:10.440 went on to a testosterone treatment,

NOTE Confidence: 0.862175963333333

00:55:10.440 --> 00:55:12.800 completely resolved in their symptoms

NOTE Confidence: 0.862175963333333

00:55:12.800 --> 00:55:15.678 and then when the testosterone levels

NOTE Confidence: 0.862175963333333

00:55:15.678 --> 00:55:17.878 were reduced for the treatment,

NOTE Confidence: 0.862175963333333

00:55:17.880 --> 00:55:19.650 they went back back onto the

NOTE Confidence: 0.862175963333333

00:55:19.650 --> 00:55:21.732 sort of original symptoms.

NOTE Confidence: 0.862175963333333

00:55:21.732 --> 00:55:24.705 So we know that there's anecdotal

NOTE Confidence: 0.862175963333333

00:55:24.705 --> 00:55:26.779 evidence of cause and effect,

NOTE Confidence: 0.862175963333333

00:55:26.779 --> 00:55:30.120 but obviously you know it's just end of one,

NOTE Confidence: 0.862175963333333

00:55:30.120 --> 00:55:32.400 but that that's sort of the the kind

NOTE Confidence: 0.862175963333333

00:55:32.400 --> 00:55:34.276 of driving force is by learning

NOTE Confidence: 0.862175963333333

00:55:34.276 --> 00:55:36.452 about these types of anecdotes from

NOTE Confidence: 0.862175963333333

00:55:36.452 --> 00:55:39.714 patients and really kind of trying to

NOTE Confidence: 0.862175963333333

00:55:39.714 --> 00:55:42.400 understand that at the population level.

NOTE Confidence: 0.862175963333333

00:55:42.400 --> 00:55:43.040 So yes,

NOTE Confidence: 0.862175963333333

00:55:43.040 --> 00:55:45.280 I think there may even be a

NOTE Confidence: 0.862175963333333

00:55:45.280 --> 00:55:46.492 cause and effect there,

NOTE Confidence: 0.862175963333333

00:55:46.492 --> 00:55:48.007 but something we really need

NOTE Confidence: 0.862175963333333

00:55:48.007 --> 00:55:49.636 to do a large scale study,

NOTE Confidence: 0.924300635

00:55:50.600 --> 00:55:51.302 yeah, awesome.

NOTE Confidence: 0.924300635

00:55:51.302 --> 00:55:53.759 And I think we'll probably only have

NOTE Confidence: 0.924300635

00:55:53.759 --> 00:55:55.694 time for one more question just

NOTE Confidence: 0.924300635

00:55:55.694 --> 00:55:57.038 to make sure we have, you know,

NOTE Confidence: 0.924300635

00:55:57.040 --> 00:55:58.640 we respect Doctor Osaki's time,

NOTE Confidence: 0.924300635

00:55:58.640 --> 00:56:00.272 but the next question that was

NOTE Confidence: 0.924300635

00:56:00.272 --> 00:56:01.752 on the list is, you know,

NOTE Confidence: 0.924300635

00:56:01.752 --> 00:56:03.320 thank you for your work on long COVID.

NOTE Confidence: 0.924300635

00:56:03.320 --> 00:56:05.385 Do you find that individual

NOTE Confidence: 0.924300635

00:56:05.385 --> 00:56:06.752 participants had a combination of

NOTE Confidence: 0.924300635

00:56:06.752 --> 00:56:08.454 the findings from each of the four

NOTE Confidence: 0.924300635

00:56:08.454 --> 00:56:09.994 root causes and or do you think,

NOTE Confidence: 0.924300635

00:56:10.000 --> 00:56:11.430 you know, maybe there's certain

NOTE Confidence: 0.924300635

00:56:11.430 --> 00:56:12.860 individuals who have a greater

NOTE Confidence: 0.924300635

00:56:12.910 --> 00:56:14.476 dominance of 1 cause over another?

NOTE Confidence: 0.959418896666667

00:56:15.240 --> 00:56:17.718 Yeah, that's definitely our next step.

NOTE Confidence: 0.959418896666667

00:56:17.720 --> 00:56:20.177 I mean we we have you know like 100

NOTE Confidence: 0.959418896666667

00:56:20.177 --> 00:56:22.313 people in the Mylan COVID study which

NOTE Confidence: 0.959418896666667

00:56:22.313 --> 00:56:25.011 is a little bit too small to start

NOTE Confidence: 0.959418896666667

00:56:25.011 --> 00:56:27.159 doing this kind of cluster analysis.

NOTE Confidence: 0.959418896666667

00:56:27.160 --> 00:56:31.878 But cortisol reduction was a pretty uniform,

NOTE Confidence: 0.959418896666667

00:56:31.880 --> 00:56:33.810 so that that that's probably

NOTE Confidence: 0.959418896666667

00:56:33.810 --> 00:56:35.354 happening in most people.

NOTE Confidence: 0.959418896666667

00:56:35.360 --> 00:56:37.028 But the persistent virus,

NOTE Confidence: 0.959418896666667

00:56:37.028 --> 00:56:39.113 persistent source could be two

NOTE Confidence: 0.959418896666667

00:56:39.113 --> 00:56:41.001 again it may be happening in

NOTE Confidence: 0.959418896666667

00:56:41.001 --> 00:56:43.320 like a third 40% of the people.

00:56:43.320 --> 00:56:44.972 Ebb reactivation happening mostly

00:56:44.972 --> 00:56:48.000 in females and not in every female.

00:56:48.000 --> 00:56:50.198 So you start to see these clusters,

00:56:50.200 --> 00:56:52.300 but you know there's definitely

00:56:52.300 --> 00:56:53.184 overlapping as well.

00:56:53.184 --> 00:56:55.040 So it's not that one person has one

00:56:55.097 --> 00:56:56.837 and the other person has another.

00:56:56.840 --> 00:56:58.440 It's it's an overlapping cluster.

00:56:58.440 --> 00:57:01.800 But we're starting to see these separate.

00:57:01.800 --> 00:57:03.228 We need thousands of people to be

00:57:03.228 --> 00:57:04.919 able to do that cluster analysis.

00:57:04.920 --> 00:57:07.356 But we're hoping to get there.

00:57:07.360 --> 00:57:07.600 Yeah,

00:57:08.000 --> 00:57:09.374 awesome. And we're just out of

00:57:09.374 --> 00:57:11.228 time and we're very sorry that we

00:57:11.228 --> 00:57:12.713 couldn't answer every single question,

NOTE Confidence: 0.875528222222222

00:57:12.720 --> 00:57:14.640 but want to thank everyone for

NOTE Confidence: 0.875528222222222

00:57:14.640 --> 00:57:15.920 joining during their lunch time today.

NOTE Confidence: 0.875528222222222

00:57:15.920 --> 00:57:17.607 And thank you for those of you

NOTE Confidence: 0.875528222222222

00:57:17.607 --> 00:57:19.239 who asked such great questions.

NOTE Confidence: 0.875528222222222

00:57:19.240 --> 00:57:20.400 And then thank you again,

NOTE Confidence: 0.875528222222222

00:57:20.400 --> 00:57:22.040 Doctor Saki, for joining us.

NOTE Confidence: 0.875528222222222

00:57:22.040 --> 00:57:23.064 That was a very,

NOTE Confidence: 0.875528222222222

00:57:23.064 --> 00:57:24.088 very great presentation and

NOTE Confidence: 0.875528222222222

00:57:24.088 --> 00:57:25.746 we're glad that please join us.

NOTE Confidence: 0.875528222222222

00:57:25.746 --> 00:57:27.558 If anyone has any additional questions,

NOTE Confidence: 0.875528222222222

00:57:27.560 --> 00:57:28.960 they can always contact her.

NOTE Confidence: 0.875528222222222

00:57:28.960 --> 00:57:29.688 But otherwise,

NOTE Confidence: 0.875528222222222

00:57:29.688 --> 00:57:32.236 have a great rest of your Thursday

NOTE Confidence: 0.875528222222222

00:57:32.236 --> 00:57:33.700 and and a great weekend.

NOTE Confidence: 0.875528222222222

00:57:33.700 --> 00:57:34.800 Thank you so much.

NOTE Confidence: 0.5297263625

00:57:35.480 --> 00:57:37.000 Thank you. Bye, bye.