

WEBVTT

NOTE duration: "00:12:17.960"

NOTE Confidence: 0.99750054

00:00:01.040 --> 00:00:02.820 Great. So I'm excited to

NOTE Confidence: 0.93343914

00:00:03.360 --> 00:00:05.120 kick off with, talk about

NOTE Confidence: 0.93343914

00:00:05.120 --> 00:00:06.420 the work in my laboratory.

NOTE Confidence: 0.9851041

00:00:07.040 --> 00:00:09.059 And and, with the ambitious

NOTE Confidence: 0.9851041

00:00:09.200 --> 00:00:10.660 goal to decode

NOTE Confidence: 0.93246746

00:00:11.200 --> 00:00:11.860 and simulate

NOTE Confidence: 0.9840764

00:00:12.535 --> 00:00:14.395 the genetic software of Parkinson's

NOTE Confidence: 0.9840764

00:00:14.455 --> 00:00:16.375 disease. We are very grateful

NOTE Confidence: 0.9840764

00:00:16.375 --> 00:00:17.735 to our sponsors. This is

NOTE Confidence: 0.9840764

00:00:17.735 --> 00:00:19.755 really a team effort. Parkinson's

NOTE Confidence: 0.9840764

00:00:19.975 --> 00:00:20.475 disease

NOTE Confidence: 0.9890219

00:00:20.855 --> 00:00:22.395 is a very important,

NOTE Confidence: 0.97626925

00:00:23.095 --> 00:00:25.095 problem. There it's actually now

NOTE Confidence: 0.97626925

00:00:25.095 --> 00:00:26.314 the fastest growing

NOTE Confidence: 0.9517886

00:00:26.810 --> 00:00:28.270 brain disease in the world,
NOTE Confidence: 0.9947702

00:00:28.730 --> 00:00:29.230 outpacing,
NOTE Confidence: 0.9965573

00:00:29.930 --> 00:00:31.710 the growth rates of Alzheimer's
NOTE Confidence: 0.9965573

00:00:31.770 --> 00:00:32.270 disease.
NOTE Confidence: 0.9367724

00:00:32.650 --> 00:00:33.770 There are ten million people
NOTE Confidence: 0.9367724

00:00:33.770 --> 00:00:35.370 with Parkinson's disease in the
NOTE Confidence: 0.9367724

00:00:35.370 --> 00:00:37.210 world today, and this in
NOTE Confidence: 0.9367724

00:00:37.370 --> 00:00:38.970 by some estimates, this number
NOTE Confidence: 0.9367724

00:00:38.970 --> 00:00:40.409 may increase to twenty five
NOTE Confidence: 0.9367724

00:00:40.409 --> 00:00:42.515 millions in in twenty fifty.
NOTE Confidence: 0.90301794

00:00:42.975 --> 00:00:44.755 And the burden for patients
NOTE Confidence: 0.90301794

00:00:44.815 --> 00:00:46.335 and their families and the
NOTE Confidence: 0.90301794

00:00:46.335 --> 00:00:47.615 health care costs are an
NOTE Confidence: 0.90301794

00:00:47.854 --> 00:00:48.354 enormous.
NOTE Confidence: 0.77912855

00:00:49.055 --> 00:00:49.795 And today's
NOTE Confidence: 0.99567443

00:00:50.255 --> 00:00:50.755 medicine

NOTE Confidence: 0.99758565
00:00:51.534 --> 00:00:52.995 does not stop the disease.
NOTE Confidence: 0.9686017
00:00:53.810 --> 00:00:54.710 It is reactive,
NOTE Confidence: 0.99928504
00:00:55.170 --> 00:00:56.550 and it treats patients
NOTE Confidence: 0.9986016
00:00:57.010 --> 00:00:58.290 as if they were all
NOTE Confidence: 0.9986016
00:00:58.290 --> 00:00:58.870 the same.
NOTE Confidence: 0.9747322
00:01:00.530 --> 00:01:02.450 So we want to change
NOTE Confidence: 0.9747322
00:01:02.450 --> 00:01:03.270 this paradigm.
NOTE Confidence: 0.98705465
00:01:03.890 --> 00:01:05.430 And and the big question
NOTE Confidence: 0.98705465
00:01:05.650 --> 00:01:07.250 that we're trying to tackle
NOTE Confidence: 0.98705465
00:01:07.250 --> 00:01:08.550 is, can we develop
NOTE Confidence: 0.9836012
00:01:09.090 --> 00:01:10.365 a predictive,
NOTE Confidence: 0.9801163
00:01:11.545 --> 00:01:12.045 precise,
NOTE Confidence: 0.99730265
00:01:12.905 --> 00:01:13.725 and preventive
NOTE Confidence: 0.96687794
00:01:14.185 --> 00:01:16.125 medicine for Parkinson's disease?
NOTE Confidence: 0.9985766
00:01:16.825 --> 00:01:18.505 And to to make this
NOTE Confidence: 0.9985766

00:01:18.505 --> 00:01:19.005 possible,
NOTE Confidence: 0.98572
00:01:19.545 --> 00:01:20.584 we are we have set
NOTE Confidence: 0.98572
00:01:20.584 --> 00:01:22.345 ourselves a very ambitious goal,
NOTE Confidence: 0.98572
00:01:22.345 --> 00:01:23.545 and that is to make,
NOTE Confidence: 0.98572
00:01:23.785 --> 00:01:26.110 digital twins of Parkinson's brain
NOTE Confidence: 0.98572
00:01:26.110 --> 00:01:27.729 cells and and Parkinson's,
NOTE Confidence: 0.9794282
00:01:29.549 --> 00:01:30.049 patients.
NOTE Confidence: 0.97649306
00:01:30.430 --> 00:01:31.310 And so how are we
NOTE Confidence: 0.97649306
00:01:31.310 --> 00:01:32.290 going about this?
NOTE Confidence: 0.8378207
00:01:35.869 --> 00:01:37.005 And under the hood
NOTE Confidence: 0.95557374
00:01:37.564 --> 00:01:39.185 are, ten multimodal,
NOTE Confidence: 0.8350957
00:01:39.564 --> 00:01:40.064 multiomics,
NOTE Confidence: 0.9626843
00:01:41.244 --> 00:01:41.744 technologies.
NOTE Confidence: 0.98209286
00:01:42.844 --> 00:01:44.524 We're doing short and and
NOTE Confidence: 0.98209286
00:01:44.524 --> 00:01:45.645 long single,
NOTE Confidence: 0.97503424
00:01:46.125 --> 00:01:48.064 read sequencing of single cells.

NOTE Confidence: 0.97503424
00:01:48.284 --> 00:01:49.905 We've done about a million.
NOTE Confidence: 0.96183544
00:01:50.210 --> 00:01:52.130 We're we're going moving towards
NOTE Confidence: 0.96183544
00:01:52.130 --> 00:01:52.869 ten million.
NOTE Confidence: 0.9740092
00:01:53.329 --> 00:01:54.789 We do spatial transcriptomics,
NOTE Confidence: 0.95487565
00:01:56.289 --> 00:01:57.649 on the spot level and
NOTE Confidence: 0.95487565
00:01:57.649 --> 00:01:59.350 on the cellular and subcellular
NOTE Confidence: 0.95487565
00:01:59.570 --> 00:02:01.189 level, with the xenon,
NOTE Confidence: 0.96637976
00:02:02.049 --> 00:02:04.005 looking at ATAC seq for
NOTE Confidence: 0.96637976
00:02:04.005 --> 00:02:06.085 open chromatin and whole genome
NOTE Confidence: 0.96637976
00:02:06.085 --> 00:02:06.585 sequences.
NOTE Confidence: 0.9639659
00:02:07.685 --> 00:02:09.125 And we're integrating all of
NOTE Confidence: 0.9639659
00:02:09.125 --> 00:02:10.105 that. And
NOTE Confidence: 0.9689323
00:02:10.805 --> 00:02:12.585 so what are the components
NOTE Confidence: 0.9852073
00:02:12.965 --> 00:02:13.625 to develop,
NOTE Confidence: 0.9890885
00:02:14.085 --> 00:02:15.845 digital twins of of brain
NOTE Confidence: 0.9890885

00:02:15.845 --> 00:02:17.044 cells? Well, number one, we

NOTE Confidence: 0.9890885

00:02:17.044 --> 00:02:17.764 need to know all the

NOTE Confidence: 0.9890885

00:02:17.764 --> 00:02:19.710 brain cells. So far, we

NOTE Confidence: 0.9890885

00:02:19.710 --> 00:02:20.530 have cataloged

NOTE Confidence: 0.9961831

00:02:20.830 --> 00:02:21.330 ninety

NOTE Confidence: 0.9542935

00:02:21.790 --> 00:02:22.110 two,

NOTE Confidence: 0.9991541

00:02:22.830 --> 00:02:23.730 cell types

NOTE Confidence: 0.9629688

00:02:24.030 --> 00:02:25.470 based on the sequencing of

NOTE Confidence: 0.9629688

00:02:25.470 --> 00:02:26.850 a million brain cells.

NOTE Confidence: 0.9542314

00:02:32.035 --> 00:02:33.715 And and we have started

NOTE Confidence: 0.9542314

00:02:33.715 --> 00:02:34.035 to map,

NOTE Confidence: 0.9089155

00:02:35.475 --> 00:02:36.775 the the

NOTE Confidence: 0.93634856

00:02:37.075 --> 00:02:38.835 the brain space, the layers,

NOTE Confidence: 0.93634856

00:02:38.835 --> 00:02:40.535 and and the spatial niches,

NOTE Confidence: 0.93733585

00:02:41.315 --> 00:02:42.915 to which the cell types,

NOTE Confidence: 0.93733585

00:02:43.235 --> 00:02:44.215 can be localized.

NOTE Confidence: 0.8107358
00:02:44.915 --> 00:02:45.235 And,
NOTE Confidence: 0.9013198
00:02:46.330 --> 00:02:48.490 doctor Junjun Dong will delve
NOTE Confidence: 0.9013198
00:02:48.490 --> 00:02:49.230 into this,
NOTE Confidence: 0.95288926
00:02:50.090 --> 00:02:51.450 in much more detail in
NOTE Confidence: 0.95288926
00:02:51.450 --> 00:02:52.250 in in a in a
NOTE Confidence: 0.95288926
00:02:52.250 --> 00:02:52.750 second.
NOTE Confidence: 0.9924328
00:02:53.290 --> 00:02:55.130 But here here is sort
NOTE Confidence: 0.9924328
00:02:55.130 --> 00:02:56.569 of an initial version of
NOTE Confidence: 0.9924328
00:02:56.569 --> 00:02:58.665 the integration of cells and
NOTE Confidence: 0.9924328
00:02:58.665 --> 00:02:59.165 space,
NOTE Confidence: 0.9755908
00:02:59.785 --> 00:03:01.965 done by Jacob Parker, who
NOTE Confidence: 0.9259412
00:03:02.264 --> 00:03:03.224 is somewhere here.
NOTE Confidence: 0.6158551
00:03:03.544 --> 00:03:04.285 They are,
NOTE Confidence: 0.99967134
00:03:05.305 --> 00:03:05.805 showing
NOTE Confidence: 0.9417204
00:03:06.185 --> 00:03:07.325 how these different
NOTE Confidence: 0.99969935

00:03:08.185 --> 00:03:09.005 cell types
NOTE Confidence: 0.9709679
00:03:09.465 --> 00:03:09.965 localize
NOTE Confidence: 0.9895477
00:03:10.720 --> 00:03:12.560 to specific layers in the
NOTE Confidence: 0.9895477
00:03:12.560 --> 00:03:14.580 temporal cortex or to specific
NOTE Confidence: 0.9895477
00:03:14.720 --> 00:03:15.220 niches,
NOTE Confidence: 0.9837132
00:03:16.080 --> 00:03:17.440 in in in the human
NOTE Confidence: 0.9837132
00:03:17.440 --> 00:03:17.940 midbrain.
NOTE Confidence: 0.9691836
00:03:19.760 --> 00:03:20.959 So what can we do
NOTE Confidence: 0.9691836
00:03:20.959 --> 00:03:22.605 with this Atlas? Well,
NOTE Confidence: 0.9829967
00:03:23.245 --> 00:03:24.685 number one, we can,
NOTE Confidence: 0.85142386
00:03:25.245 --> 00:03:26.864 lay out all this multi,
NOTE Confidence: 0.75400066
00:03:28.364 --> 00:03:28.864 omic
NOTE Confidence: 0.9224175
00:03:29.325 --> 00:03:31.885 datasets and integrate them, and
NOTE Confidence: 0.9224175
00:03:31.885 --> 00:03:32.525 we can,
NOTE Confidence: 0.965478
00:03:33.084 --> 00:03:35.265 see how disease progresses,
NOTE Confidence: 0.96727616
00:03:36.129 --> 00:03:37.430 in this dynamic,

NOTE Confidence: 0.9979405
00:03:38.129 --> 00:03:39.430 view of transcriptional
NOTE Confidence: 0.9338324
00:03:39.810 --> 00:03:40.310 changes.
NOTE Confidence: 0.98976624
00:03:41.489 --> 00:03:41.970 And,
NOTE Confidence: 0.9112124
00:03:42.370 --> 00:03:43.810 again, the next talk will
NOTE Confidence: 0.9112124
00:03:43.810 --> 00:03:44.870 look at the dynamic
NOTE Confidence: 0.99804586
00:03:45.250 --> 00:03:47.430 evolution of the disease across
NOTE Confidence: 0.99804586
00:03:47.569 --> 00:03:49.110 space and time.
NOTE Confidence: 0.9992113
00:03:49.855 --> 00:03:51.395 We can also link this
NOTE Confidence: 0.9992113
00:03:51.535 --> 00:03:52.275 to pathology
NOTE Confidence: 0.9968339
00:03:53.535 --> 00:03:55.075 and to clinical phenotypes
NOTE Confidence: 0.97911114
00:03:55.535 --> 00:03:57.375 with the ultimate goal to
NOTE Confidence: 0.97911114
00:03:57.375 --> 00:03:57.875 use
NOTE Confidence: 0.81064
00:03:58.335 --> 00:03:58.835 this,
NOTE Confidence: 0.92358494
00:03:59.855 --> 00:04:00.355 molecular
NOTE Confidence: 0.9985324
00:04:00.655 --> 00:04:01.155 signatures
NOTE Confidence: 0.93412423

00:04:01.695 --> 00:04:03.315 to predict and prevent,
NOTE Confidence: 0.94944847

00:04:04.400 --> 00:04:06.400 disease in in patients and
NOTE Confidence: 0.94944847

00:04:06.400 --> 00:04:07.700 prevent this progression.
NOTE Confidence: 0.9906093

00:04:08.560 --> 00:04:10.580 So but one of the
NOTE Confidence: 0.9981804

00:04:11.280 --> 00:04:13.140 very cool applications
NOTE Confidence: 0.9819177

00:04:14.080 --> 00:04:15.860 of this prototype
NOTE Confidence: 0.9611335

00:04:16.160 --> 00:04:18.020 digital twins is
NOTE Confidence: 0.99589777

00:04:18.400 --> 00:04:19.300 that it
NOTE Confidence: 0.97993547

00:04:19.815 --> 00:04:20.315 allows
NOTE Confidence: 0.9944011

00:04:20.775 --> 00:04:23.195 to infer genome function,
NOTE Confidence: 0.943906

00:04:24.455 --> 00:04:26.154 in particular brain cells.
NOTE Confidence: 0.9790042

00:04:27.015 --> 00:04:29.255 And and and so this
NOTE Confidence: 0.9790042

00:04:29.255 --> 00:04:29.755 allows
NOTE Confidence: 0.8782221

00:04:30.135 --> 00:04:30.635 to
NOTE Confidence: 0.942743

00:04:31.175 --> 00:04:32.795 look at the genome sequence,
NOTE Confidence: 0.942743

00:04:33.095 --> 00:04:34.635 input the genome sequence,

NOTE Confidence: 0.8987461
00:04:35.029 --> 00:04:36.570 and have as a readout
NOTE Confidence: 0.8987461
00:04:36.790 --> 00:04:37.450 a prediction
NOTE Confidence: 0.99958265
00:04:38.150 --> 00:04:40.650 of RNA changes in specific
NOTE Confidence: 0.99252677
00:04:41.110 --> 00:04:41.930 brain cells.
NOTE Confidence: 0.89766574
00:04:42.950 --> 00:04:43.430 And,
NOTE Confidence: 0.9983224
00:04:45.029 --> 00:04:45.910 to do this, what are
NOTE Confidence: 0.9983224
00:04:45.910 --> 00:04:47.510 the components that we need?
NOTE Confidence: 0.9983224
00:04:47.510 --> 00:04:49.029 Well, we need to we
NOTE Confidence: 0.9983224
00:04:49.029 --> 00:04:49.850 need to
NOTE Confidence: 0.9656334
00:04:50.845 --> 00:04:51.345 have,
NOTE Confidence: 0.9703225
00:04:52.125 --> 00:04:53.505 all the DNA variants.
NOTE Confidence: 0.9987904
00:04:54.525 --> 00:04:55.964 We want we need to
NOTE Confidence: 0.9987904
00:04:55.964 --> 00:04:57.505 wire them to the RNA
NOTE Confidence: 0.9987904
00:04:57.565 --> 00:04:58.065 changes
NOTE Confidence: 0.91507465
00:04:59.805 --> 00:05:01.425 in specific brain cells,
NOTE Confidence: 0.97518706

00:05:03.089 --> 00:05:04.230 combine convergent,
NOTE Confidence: 0.9500965

00:05:05.170 --> 00:05:07.730 pathways to identify processes, and
NOTE Confidence: 0.9500965

00:05:07.730 --> 00:05:08.870 thereby, delineate
NOTE Confidence: 0.92656237

00:05:09.330 --> 00:05:11.890 the gene regulatory networks from
NOTE Confidence: 0.92656237

00:05:11.890 --> 00:05:12.950 DNA variants
NOTE Confidence: 0.96614796

00:05:13.490 --> 00:05:15.190 to, cellular processes.
NOTE Confidence: 0.9906643

00:05:16.375 --> 00:05:17.915 And if we are successful
NOTE Confidence: 0.9906643

00:05:18.055 --> 00:05:19.835 with this, it will give
NOTE Confidence: 0.9974948

00:05:20.214 --> 00:05:20.794 us targets
NOTE Confidence: 0.9637033

00:05:21.654 --> 00:05:22.135 to,
NOTE Confidence: 0.804815

00:05:23.014 --> 00:05:24.395 prevent that patient's
NOTE Confidence: 0.9934526

00:05:25.255 --> 00:05:26.235 disease progresses,
NOTE Confidence: 0.99438065

00:05:28.294 --> 00:05:29.435 to slow movements,
NOTE Confidence: 0.9556078

00:05:30.089 --> 00:05:31.710 motor Parkinson's, and cognitive
NOTE Confidence: 0.9546657

00:05:32.010 --> 00:05:33.310 decline, and instead
NOTE Confidence: 0.8716204

00:05:34.170 --> 00:05:35.070 turn patients,

NOTE Confidence: 0.8886967
00:05:36.650 --> 00:05:38.029 into slow progressors
NOTE Confidence: 0.9939653
00:05:38.330 --> 00:05:39.310 that are able
NOTE Confidence: 0.979638
00:05:39.610 --> 00:05:41.770 to enjoy an awesome quality
NOTE Confidence: 0.979638
00:05:41.770 --> 00:05:43.390 of life and play golf,
NOTE Confidence: 0.9729293
00:05:43.854 --> 00:05:46.175 for fifteen years and, enjoy
NOTE Confidence: 0.9729293
00:05:46.175 --> 00:05:47.555 time with the grandchildren.
NOTE Confidence: 0.9989875
00:05:48.574 --> 00:05:49.074 So
NOTE Confidence: 0.9622766
00:05:49.935 --> 00:05:51.375 what do we know about
NOTE Confidence: 0.9622766
00:05:51.375 --> 00:05:52.354 the noncode
NOTE Confidence: 0.9329948
00:05:52.654 --> 00:05:54.814 about the, DNA variants? What
NOTE Confidence: 0.9329948
00:05:54.814 --> 00:05:56.414 can we input in into
NOTE Confidence: 0.9329948
00:05:56.414 --> 00:05:57.235 our prototype?
NOTE Confidence: 0.8208291
00:06:00.130 --> 00:06:01.190 They're in principle
NOTE Confidence: 0.7284587
00:06:01.650 --> 00:06:02.150 two
NOTE Confidence: 0.97040206
00:06:02.690 --> 00:06:04.130 two types of,
NOTE Confidence: 0.8623307

00:06:05.650 --> 00:06:07.510 two two ways the genome
NOTE Confidence: 0.8623307

00:06:07.810 --> 00:06:10.150 of functions functions. One is
NOTE Confidence: 0.8623307

00:06:10.290 --> 00:06:11.270 sequence modulation,
NOTE Confidence: 0.99823594

00:06:13.089 --> 00:06:13.589 where
NOTE Confidence: 0.9992422

00:06:14.395 --> 00:06:14.895 mutations
NOTE Confidence: 0.9841586

00:06:15.675 --> 00:06:17.695 change the protein coding sequence.
NOTE Confidence: 0.9841586

00:06:17.915 --> 00:06:19.375 And that's the case in
NOTE Confidence: 0.9841586

00:06:19.675 --> 00:06:20.175 Mendelian
NOTE Confidence: 0.9663924

00:06:20.475 --> 00:06:22.475 forms of the disease that
NOTE Confidence: 0.9663924

00:06:22.475 --> 00:06:24.315 comprise about three percent of
NOTE Confidence: 0.9663924

00:06:24.315 --> 00:06:25.695 all Parkinson's patients.
NOTE Confidence: 0.98859954

00:06:26.074 --> 00:06:26.315 And,
NOTE Confidence: 0.7071365

00:06:26.875 --> 00:06:27.695 Shri Ganachandra
NOTE Confidence: 0.94810146

00:06:28.430 --> 00:06:30.029 and Pietro de Camille will
NOTE Confidence: 0.94810146

00:06:30.029 --> 00:06:31.710 take a deep dive on
NOTE Confidence: 0.94810146

00:06:31.710 --> 00:06:32.690 some of these,

NOTE Confidence: 0.952004
00:06:33.150 --> 00:06:33.650 familial
NOTE Confidence: 0.9991671
00:06:34.110 --> 00:06:34.610 genes.
NOTE Confidence: 0.99946463
00:06:35.710 --> 00:06:36.210 However,
NOTE Confidence: 0.99802804
00:06:37.310 --> 00:06:38.850 most Parkinson's patients
NOTE Confidence: 0.98987895
00:06:39.630 --> 00:06:41.630 don't have a mutation that
NOTE Confidence: 0.98987895
00:06:41.630 --> 00:06:43.010 changes protein sequence.
NOTE Confidence: 0.9914043
00:06:43.365 --> 00:06:43.865 Instead,
NOTE Confidence: 0.99370193
00:06:44.165 --> 00:06:46.085 there are seven thousand fifty
NOTE Confidence: 0.99370193
00:06:46.085 --> 00:06:46.585 seven
NOTE Confidence: 0.8588473
00:06:46.885 --> 00:06:48.665 non coding DNA variants,
NOTE Confidence: 0.993061
00:06:49.365 --> 00:06:51.305 linked to Parkinson's disease.
NOTE Confidence: 0.99615294
00:06:52.805 --> 00:06:54.005 They account for up to
NOTE Confidence: 0.99615294
00:06:54.005 --> 00:06:55.445 thirty six percent of the
NOTE Confidence: 0.99615294
00:06:55.445 --> 00:06:56.505 genetic heritability
NOTE Confidence: 0.88836336
00:06:57.205 --> 00:06:57.945 of the disease.
NOTE Confidence: 0.99767923

00:06:58.819 --> 00:06:59.960 But the key question
NOTE Confidence: 0.90549386

00:07:00.500 --> 00:07:01.800 is, how do these function?
NOTE Confidence: 0.99494743

00:07:03.060 --> 00:07:04.680 And, what we have previously
NOTE Confidence: 0.99494743

00:07:04.819 --> 00:07:05.319 seen
NOTE Confidence: 0.9116438

00:07:05.860 --> 00:07:07.460 is that these non coding
NOTE Confidence: 0.9116438

00:07:07.460 --> 00:07:09.780 variants are highly enriched in,
NOTE Confidence: 0.9116438

00:07:10.259 --> 00:07:11.080 cis regulatory
NOTE Confidence: 0.9238937

00:07:11.380 --> 00:07:11.880 regions,
NOTE Confidence: 0.78574264

00:07:12.340 --> 00:07:13.720 of the genome and enhances
NOTE Confidence: 0.9073528

00:07:14.315 --> 00:07:15.835 and promoters. And so we
NOTE Confidence: 0.9073528

00:07:15.835 --> 00:07:16.975 therefore hypothesize
NOTE Confidence: 0.99444336

00:07:17.995 --> 00:07:18.495 that
NOTE Confidence: 0.8182818

00:07:19.115 --> 00:07:20.095 really the key,
NOTE Confidence: 0.99793386

00:07:21.755 --> 00:07:22.255 function
NOTE Confidence: 0.9833769

00:07:22.715 --> 00:07:24.815 genome function perturbed in Parkinson's
NOTE Confidence: 0.9833769

00:07:24.955 --> 00:07:25.455 disease

NOTE Confidence: 0.97966194
00:07:25.755 --> 00:07:27.135 might be modulation
NOTE Confidence: 0.9985623
00:07:27.675 --> 00:07:29.135 of RNA quantity
NOTE Confidence: 0.8836714
00:07:29.789 --> 00:07:31.169 based on cis regulatory,
NOTE Confidence: 0.92953265
00:07:31.949 --> 00:07:33.970 effects of this noncoding variant.
NOTE Confidence: 0.98278606
00:07:34.830 --> 00:07:36.110 How how can we treat
NOTE Confidence: 0.98278606
00:07:36.110 --> 00:07:38.210 this with precision drugs? Obviously,
NOTE Confidence: 0.98278606
00:07:38.349 --> 00:07:39.629 a lot more to do,
NOTE Confidence: 0.98278606
00:07:39.629 --> 00:07:40.830 but we do have some
NOTE Confidence: 0.98278606
00:07:40.830 --> 00:07:41.330 exciting,
NOTE Confidence: 0.9720496
00:07:41.870 --> 00:07:42.930 initial results.
NOTE Confidence: 0.95850426
00:07:43.445 --> 00:07:44.805 And most of all, we
NOTE Confidence: 0.95850426
00:07:44.805 --> 00:07:45.925 have what I think is
NOTE Confidence: 0.95850426
00:07:45.925 --> 00:07:47.545 really a cool way
NOTE Confidence: 0.97005695
00:07:47.925 --> 00:07:49.925 to try our best to,
NOTE Confidence: 0.97005695
00:07:50.165 --> 00:07:51.945 bring new drugs to patients
NOTE Confidence: 0.97005695

00:07:52.005 --> 00:07:53.225 as fast as possible,
NOTE Confidence: 0.9489603
00:07:53.605 --> 00:07:54.325 and that is,
NOTE Confidence: 0.93891793
00:07:55.205 --> 00:07:57.465 machine learning, big data powered,
NOTE Confidence: 0.94216347
00:07:57.970 --> 00:08:00.130 drug repurposing to teach new
NOTE Confidence: 0.94216347
00:08:00.130 --> 00:08:01.590 tricks to old drugs.
NOTE Confidence: 0.96217537
00:08:01.970 --> 00:08:03.190 This work is,
NOTE Confidence: 0.96520627
00:08:03.810 --> 00:08:05.490 performed in collaboration with the
NOTE Confidence: 0.96520627
00:08:05.490 --> 00:08:06.710 University of Burdon.
NOTE Confidence: 0.88931155
00:08:07.250 --> 00:08:09.010 The TronTrees has been a
NOTE Confidence: 0.88931155
00:08:09.010 --> 00:08:10.610 partner with us, first at
NOTE Confidence: 0.88931155
00:08:10.610 --> 00:08:12.375 Harvard and now here at
NOTE Confidence: 0.88931155
00:08:12.375 --> 00:08:13.895 the Stephen and Denise Adams
NOTE Confidence: 0.88931155
00:08:13.895 --> 00:08:14.395 Center.
NOTE Confidence: 0.9767645
00:08:14.775 --> 00:08:16.075 The way this works is,
NOTE Confidence: 0.9687419
00:08:17.895 --> 00:08:19.975 in Norway, we have,
NOTE Confidence: 0.9480904
00:08:20.775 --> 00:08:23.355 access on well curated databases

NOTE Confidence: 0.9533901
00:08:23.895 --> 00:08:25.350 for four point five million
NOTE Confidence: 0.9533901
00:08:25.350 --> 00:08:27.509 Norwegians over fifteen years with
NOTE Confidence: 0.9533901
00:08:27.509 --> 00:08:28.810 fifteen years of follow-up.
NOTE Confidence: 0.9783257
00:08:30.310 --> 00:08:32.230 There's, about seven hundred fifty
NOTE Confidence: 0.9783257
00:08:32.230 --> 00:08:33.290 million prescriptions
NOTE Confidence: 0.97539085
00:08:33.670 --> 00:08:35.589 given to these patients, and
NOTE Confidence: 0.97539085
00:08:35.589 --> 00:08:36.890 so we can now
NOTE Confidence: 0.99847347
00:08:38.405 --> 00:08:38.905 algorithmically
NOTE Confidence: 0.9927163
00:08:39.845 --> 00:08:41.145 test for associations
NOTE Confidence: 0.99638987
00:08:41.605 --> 00:08:43.365 between any drug approved in
NOTE Confidence: 0.99638987
00:08:43.365 --> 00:08:43.865 Norway
NOTE Confidence: 0.92613447
00:08:44.325 --> 00:08:44.985 and the
NOTE Confidence: 0.98529685
00:08:45.365 --> 00:08:47.385 future risk of healthy Norwegians
NOTE Confidence: 0.98529685
00:08:47.684 --> 00:08:49.845 of developing Parkinson's disease. And
NOTE Confidence: 0.98529685
00:08:49.845 --> 00:08:50.885 so you do this over
NOTE Confidence: 0.98529685

00:08:50.885 --> 00:08:52.345 and over for each drug,
NOTE Confidence: 0.97647136
00:08:52.780 --> 00:08:55.260 to identify drugs linked to
NOTE Confidence: 0.97647136
00:08:55.260 --> 00:08:56.480 reduce risk.
NOTE Confidence: 0.90591705
00:08:57.100 --> 00:08:58.720 Then we're taking these drugs
NOTE Confidence: 0.90591705
00:08:58.860 --> 00:09:01.260 into into clinical trials in
NOTE Confidence: 0.90591705
00:09:01.260 --> 00:09:02.720 a dish animal models
NOTE Confidence: 0.9727237
00:09:03.260 --> 00:09:05.179 and to medicinal chemistry. And
NOTE Confidence: 0.9727237
00:09:05.179 --> 00:09:05.679 one
NOTE Confidence: 0.9261749
00:09:06.165 --> 00:09:06.665 one,
NOTE Confidence: 0.99964553
00:09:07.125 --> 00:09:08.345 class of drugs
NOTE Confidence: 0.9972093
00:09:08.725 --> 00:09:10.084 that was very strong
NOTE Confidence: 0.9018985
00:09:10.644 --> 00:09:12.985 strongly associated with reduced risk
NOTE Confidence: 0.9683267
00:09:13.365 --> 00:09:13.845 are,
NOTE Confidence: 0.9764599
00:09:14.325 --> 00:09:15.705 asthma drugs, surprisingly.
NOTE Confidence: 0.97474897
00:09:16.165 --> 00:09:17.625 Those are beta two,
NOTE Confidence: 0.9808907
00:09:18.485 --> 00:09:18.985 adrenoreceptor

NOTE Confidence: 0.9158632
00:09:19.605 --> 00:09:20.105 agonists.
NOTE Confidence: 0.90832424
00:09:20.644 --> 00:09:22.300 And we have since shown
NOTE Confidence: 0.90832424
00:09:22.300 --> 00:09:22.959 that, actually,
NOTE Confidence: 0.9898079
00:09:23.260 --> 00:09:24.860 the longer acting they are,
NOTE Confidence: 0.9898079
00:09:24.860 --> 00:09:26.620 the more lipophilic and brain
NOTE Confidence: 0.9898079
00:09:26.620 --> 00:09:28.220 penetrant they are, the stronger
NOTE Confidence: 0.9898079
00:09:28.220 --> 00:09:29.820 the effect is. This has
NOTE Confidence: 0.9898079
00:09:29.820 --> 00:09:31.980 now been, replicated in more
NOTE Confidence: 0.9898079
00:09:31.980 --> 00:09:33.040 than eight countries
NOTE Confidence: 0.7827774
00:09:33.420 --> 00:09:34.059 and in,
NOTE Confidence: 0.99886936
00:09:35.019 --> 00:09:35.519 ten
NOTE Confidence: 0.991586
00:09:36.275 --> 00:09:38.434 toxic and genetic models of
NOTE Confidence: 0.991586
00:09:38.434 --> 00:09:39.955 Parkinson's disease. So there is
NOTE Confidence: 0.991586
00:09:39.955 --> 00:09:40.695 an association
NOTE Confidence: 0.9477188
00:09:41.395 --> 00:09:43.235 between these asthma drugs and
NOTE Confidence: 0.9477188

00:09:43.235 --> 00:09:45.735 reduced risk of Parkinson's disease.

NOTE Confidence: 0.9477188

00:09:46.035 --> 00:09:46.855 And excitingly,

NOTE Confidence: 0.8697876

00:09:47.395 --> 00:09:49.635 what Monica Sharmer in,

NOTE Confidence: 0.8726409

00:09:50.420 --> 00:09:52.040 the Adam Center and instructor

NOTE Confidence: 0.8726409

00:09:52.100 --> 00:09:53.300 in the Adam Center has

NOTE Confidence: 0.8726409

00:09:53.300 --> 00:09:54.120 found is

NOTE Confidence: 0.966682

00:09:54.500 --> 00:09:55.640 that if you use,

NOTE Confidence: 0.98039526

00:09:56.500 --> 00:09:58.500 stem cells of Parkinson's patients

NOTE Confidence: 0.98039526

00:09:58.500 --> 00:09:59.940 as as avatars in a

NOTE Confidence: 0.98039526

00:09:59.940 --> 00:10:01.460 test tube and look at

NOTE Confidence: 0.98039526

00:10:01.460 --> 00:10:02.280 the mitochondrial

NOTE Confidence: 0.78399765

00:10:02.660 --> 00:10:03.160 networks.

NOTE Confidence: 0.9375482

00:10:03.545 --> 00:10:04.605 So this is a healthy

NOTE Confidence: 0.9375482

00:10:04.665 --> 00:10:06.905 nit mitochondrial network with this

NOTE Confidence: 0.9375482

00:10:06.905 --> 00:10:08.684 nice tubular structure.

NOTE Confidence: 0.97086555

00:10:09.385 --> 00:10:11.165 In patients carrying the synuclein

NOTE Confidence: 0.97086555
00:10:11.305 --> 00:10:11.805 triplications,
NOTE Confidence: 0.96775967
00:10:12.505 --> 00:10:14.605 the mitochondrial network is busted
NOTE Confidence: 0.96775967
00:10:14.905 --> 00:10:15.785 into this,
NOTE Confidence: 0.9988659
00:10:16.985 --> 00:10:17.485 disjointed
NOTE Confidence: 0.9603322
00:10:21.429 --> 00:10:24.329 spherical forms. But treatment with
NOTE Confidence: 0.9545195
00:10:24.790 --> 00:10:25.850 beta two agonists
NOTE Confidence: 0.98561925
00:10:26.390 --> 00:10:29.130 partially restores the mitochondrial network.
NOTE Confidence: 0.98561925
00:10:29.429 --> 00:10:30.630 And in, you know, an
NOTE Confidence: 0.98561925
00:10:30.630 --> 00:10:32.250 immense body of work,
NOTE Confidence: 0.89911485
00:10:34.035 --> 00:10:36.195 Monica has shown that the
NOTE Confidence: 0.89911485
00:10:36.195 --> 00:10:37.175 beta two agonist
NOTE Confidence: 0.9837711
00:10:37.554 --> 00:10:38.054 actually
NOTE Confidence: 0.5663272
00:10:38.434 --> 00:10:38.934 affect,
NOTE Confidence: 0.9048933
00:10:39.554 --> 00:10:40.054 modulate
NOTE Confidence: 0.7819332
00:10:40.595 --> 00:10:41.654 mitochondrial respiration,
NOTE Confidence: 0.9648015

00:10:42.195 --> 00:10:42.695 remodel
NOTE Confidence: 0.98838115
00:10:43.075 --> 00:10:43.575 mitochondria
NOTE Confidence: 0.9708603
00:10:44.115 --> 00:10:45.654 to exactly counter,
NOTE Confidence: 0.9941883
00:10:46.595 --> 00:10:47.255 the effects
NOTE Confidence: 0.86076206
00:10:48.050 --> 00:10:49.990 conferred by uncoupled uncoupled,
NOTE Confidence: 0.9046357
00:10:50.370 --> 00:10:51.649 such as PM twenty d
NOTE Confidence: 0.9046357
00:10:51.649 --> 00:10:53.809 one. So so we think
NOTE Confidence: 0.9046357
00:10:53.809 --> 00:10:55.970 that these drugs actually meant
NOTE Confidence: 0.9046357
00:10:55.970 --> 00:10:56.790 to be excellent
NOTE Confidence: 0.7866179
00:10:57.570 --> 00:10:58.870 candidates for,
NOTE Confidence: 0.9928222
00:10:59.985 --> 00:11:01.445 as precision therapeutics
NOTE Confidence: 0.92644995
00:11:02.065 --> 00:11:03.985 for patients with the PM
NOTE Confidence: 0.92644995
00:11:03.985 --> 00:11:04.804 twenty one,
NOTE Confidence: 0.8969584
00:11:05.985 --> 00:11:07.825 risk variant. Here is the
NOTE Confidence: 0.8969584
00:11:07.825 --> 00:11:09.045 sea, seahorse,
NOTE Confidence: 0.8610678
00:11:10.065 --> 00:11:10.565 respirometry

NOTE Confidence: 0.8093271
00:11:10.945 --> 00:11:12.165 data where,
NOTE Confidence: 0.9959391
00:11:13.000 --> 00:11:15.340 respiration is reduced in Parkinson's
NOTE Confidence: 0.71962273
00:11:16.520 --> 00:11:17.020 neurons,
NOTE Confidence: 0.7628923
00:11:17.559 --> 00:11:19.260 be the two agonists, partially
NOTE Confidence: 0.7628923
00:11:19.400 --> 00:11:20.600 restore it here to help
NOTE Confidence: 0.7628923
00:11:20.600 --> 00:11:21.580 healthy neurons.
NOTE Confidence: 0.9755306
00:11:22.440 --> 00:11:22.920 And,
NOTE Confidence: 0.9965886
00:11:23.559 --> 00:11:24.380 with that,
NOTE Confidence: 0.9246049
00:11:25.025 --> 00:11:26.145 here's what we are ho
NOTE Confidence: 0.9246049
00:11:26.385 --> 00:11:27.505 where we are hoping to
NOTE Confidence: 0.9246049
00:11:27.505 --> 00:11:28.945 be in the future in
NOTE Confidence: 0.9246049
00:11:28.945 --> 00:11:30.705 twenty thirty four. When a
NOTE Confidence: 0.9246049
00:11:30.705 --> 00:11:32.325 patient comes to the clinic,
NOTE Confidence: 0.83666706
00:11:32.865 --> 00:11:34.645 ask the discovery engine, says
NOTE Confidence: 0.97535586
00:11:35.105 --> 00:11:36.465 the patient says, hi, discovery
NOTE Confidence: 0.97535586

00:11:36.465 --> 00:11:37.605 engine. What medication
NOTE Confidence: 0.9992911

00:11:38.385 --> 00:11:39.445 works for me?
NOTE Confidence: 0.9864311

00:11:40.050 --> 00:11:41.650 Patient inputs three drops of
NOTE Confidence: 0.9864311

00:11:41.650 --> 00:11:43.809 blood. The engine scans the
NOTE Confidence: 0.9864311

00:11:43.809 --> 00:11:45.410 genome and sucks in the
NOTE Confidence: 0.9864311

00:11:45.410 --> 00:11:46.230 health data
NOTE Confidence: 0.8658407

00:11:49.490 --> 00:11:50.450 and and spits out the
NOTE Confidence: 0.8658407

00:11:50.450 --> 00:11:53.110 result. Hi. Your bioscan suggests
NOTE Confidence: 0.8658407

00:11:53.250 --> 00:11:54.610 that gene x drives your
NOTE Confidence: 0.8658407

00:11:54.610 --> 00:11:55.510 disease progression.
NOTE Confidence: 0.9969252

00:11:55.944 --> 00:11:57.625 May I recommend the following
NOTE Confidence: 0.9969252

00:11:57.625 --> 00:11:58.125 precision,
NOTE Confidence: 0.97135997

00:11:59.065 --> 00:12:01.464 drug and precision biomarker to
NOTE Confidence: 0.97135997

00:12:01.464 --> 00:12:03.245 correct this? And don't forget
NOTE Confidence: 0.97135997

00:12:03.464 --> 00:12:04.985 to discuss this with your
NOTE Confidence: 0.97135997

00:12:04.985 --> 00:12:06.824 physician. So thank you for

NOTE Confidence: 0.97135997

00:12:06.824 --> 00:12:07.865 listening to me, and thank

NOTE Confidence: 0.97135997

00:12:07.865 --> 00:12:09.464 you, everybody in the lab

NOTE Confidence: 0.97135997

00:12:09.464 --> 00:12:10.665 and the Adam Center for

NOTE Confidence: 0.97135997

00:12:10.665 --> 00:12:12.154 this awesome work and to

NOTE Confidence: 0.97135997

00:12:12.154 --> 00:12:13.294 the ASAP team,

NOTE Confidence: 0.93165433

00:12:14.234 --> 00:12:15.274 who is working with us

NOTE Confidence: 0.93165433

00:12:15.274 --> 00:12:15.934 on that.