WEBVTT

NOTE duration:"00:55:39.6480000"

NOTE language:en-us

NOTE Confidence: 0.859560012817383

 $00:00:00.000 \rightarrow 00:00:02.370$  What you know it's 1202 or

NOTE Confidence: 0.859560012817383

 $00:00:02.370 \longrightarrow 00:00:04.780$  why don't we get started?

NOTE Confidence: 0.859560012817383

 $00:00:04.780 \longrightarrow 00:00:08.416$  And I know there are folks still logging on,

NOTE Confidence: 0.859560012817383

 $00:00:08.420 \longrightarrow 00:00:11.644$  so for those of us who are here,

NOTE Confidence: 0.859560012817383

 $00:00:11.650 \rightarrow 00:00:14.478$  thank you for joining cancer grand rounds.

NOTE Confidence: 0.859560012817383

00:00:14.480 --> 00:00:17.592 I hope all of you had a restful

NOTE Confidence: 0.859560012817383

 $00{:}00{:}17.592 \dashrightarrow 00{:}00{:}19.929$  and enjoyable Thanks giving and.

NOTE Confidence: 0.859560012817383

 $00:00:19.930 \longrightarrow 00:00:22.120$  Obviously, I know we're all

NOTE Confidence: 0.859560012817383

 $00:00:22.120 \rightarrow 00:00:24.905$  looking forward to year's end and

NOTE Confidence: 0.859560012817383

 $00:00:24.905 \longrightarrow 00:00:27.470$  hopefully celebrating a better 2021,

NOTE Confidence: 0.859560012817383

 $00{:}00{:}27.470 \dashrightarrow 00{:}00{:}30.837$  but we're really very fortunate to have

NOTE Confidence: 0.859560012817383

 $00:00:30.837 \rightarrow 00:00:33.712$  two exceptional speakers today and I'll

NOTE Confidence: 0.859560012817383

 $00:00:33.712 \rightarrow 00:00:36.418$  start by introducing our first speaker,

NOTE Confidence: 0.859560012817383

 $00:00:36.420 \rightarrow 00:00:39.320$  who frankly needs no introduction.

- NOTE Confidence: 0.859560012817383
- $00:00:39.320 \longrightarrow 00:00:41.052$  Doctor Barbara Burtness is
- NOTE Confidence: 0.859560012817383
- 00:00:41.052 --> 00:00:42.784 professor of Medicine Co,
- NOTE Confidence: 0.859560012817383
- $00:00:42.790 \longrightarrow 00:00:44.898$  leader of the Developmental
- NOTE Confidence: 0.859560012817383
- $00:00:44.898 \rightarrow 00:00:46.479$  Therapeutics research program.
- NOTE Confidence: 0.859560012817383
- $00:00:46.480 \rightarrow 00:00:49.104$  And leader of the head neck cancer program
- NOTE Confidence: 0.859560012817383
- $00:00:49.104 \rightarrow 00:00:51.270$  and Yell Barbara is internationally
- NOTE Confidence: 0.859560012817383
- $00:00:51.270 \rightarrow 00:00:54.162$  known for her leadership in clinical
- NOTE Confidence: 0.859560012817383
- $00{:}00{:}54.162 \dashrightarrow 00{:}00{:}56.001$  development and research and
- NOTE Confidence: 0.859560012817383
- $00:00:56.001 \rightarrow 00:00:58.151$  understanding the biology of heading
- NOTE Confidence: 0.859560012817383
- $00:00:58.151 \rightarrow 00:01:00.612$  that canceran among her many accolades.
- NOTE Confidence: 0.859560012817383
- $00:01:00.612 \longrightarrow 00:01:04.019$  We can add now only in the past
- NOTE Confidence: 0.859560012817383
- $00:01:04.019 \rightarrow 00:01:06.344$  month is the principle investigator
- NOTE Confidence: 0.859560012817383
- $00:01:06.344 \dashrightarrow 00:01:09.688$  of the head and Explorer of which we
- NOTE Confidence: 0.859560012817383
- 00:01:09.688 --> 00:01:12.390 are just so proud of both Barbara
- NOTE Confidence: 0.859560012817383
- $00{:}01{:}12.390 \dashrightarrow 00{:}01{:}14.880$  and the entire team being awarded
- NOTE Confidence: 0.859560012817383

 $00:01:14.880 \rightarrow 00:01:17.428$  this really coveted an elite grant.

NOTE Confidence: 0.859560012817383

 $00{:}01{:}17{.}430 \dashrightarrow 00{:}01{:}19{.}544$  Of which I think will be from

NOTE Confidence: 0.859560012817383

00:01:19.544 --> 00:01:21.689 not correct if I'm not mistaken,

NOTE Confidence: 0.859560012817383

 $00:01:21.690 \longrightarrow 00:01:23.658$  there only two head neck spores

NOTE Confidence: 0.859560012817383

 $00{:}01{:}23.660 \dashrightarrow 00{:}01{:}25.963$  now in the United States are the

NOTE Confidence: 0.859560012817383

 $00{:}01{:}25{.}963 \dashrightarrow 00{:}01{:}27{.}599$  leader of one of them,

NOTE Confidence: 0.859560012817383

 $00:01:27.600 \rightarrow 00:01:29.742$  which is an extraordinary distinction for

NOTE Confidence: 0.859560012817383

 $00:01:29.742 \longrightarrow 00:01:32.516$  the people who work in this space at Yale.

NOTE Confidence: 0.859560012817383

 $00:01:32.520 \longrightarrow 00:01:34.326$  So Barbara was kind enough to

NOTE Confidence: 0.859560012817383

 $00:01:34.326 \rightarrow 00:01:36.650$  share with us the work she's doing

NOTE Confidence: 0.859560012817383

 $00{:}01{:}36.650 \dashrightarrow 00{:}01{:}38.744$  on head neck cancer and for ever.

NOTE Confidence: 0.859560012817383

 $00:01:38.750 \longrightarrow 00:01:40.058$  Thank you for joining

NOTE Confidence: 0.823722958564758

 $00:01:40.060 \rightarrow 00:01:41.245$  us today. Well,

NOTE Confidence: 0.823722958564758

 $00:01:41.245 \dashrightarrow 00:01:44.010$  thank you for the invitation and for.

NOTE Confidence: 0.823722958564758

 $00:01:44.010 \dashrightarrow 00:01:46.946$  All the support that's gotten us this far.

NOTE Confidence: 0.823722958564758

 $00:01:46.950 \longrightarrow 00:01:49.454$  So what I wanted to do was talk

00:01:49.454 --> 00:01:52.078 about P53 mutated head neck cancer,

NOTE Confidence: 0.823722958564758

 $00:01:52.080 \longrightarrow 00:01:54.288$  which is something I have a

NOTE Confidence: 0.823722958564758

 $00:01:54.288 \longrightarrow 00:01:55.392$  longstanding interest in.

NOTE Confidence: 0.823722958564758

00:01:55.400 --> 00:01:59.992 And. Obviously, P 53 is a very

NOTE Confidence: 0.823722958564758

 $00:01:59.992 \dashrightarrow 00:02:02.670$  critical tumor suppressor gene.

NOTE Confidence: 0.823722958564758

 $00:02:02.670 \longrightarrow 00:02:05.486$  It's meant to be the cells way of

NOTE Confidence: 0.823722958564758

 $00:02:05.486 \rightarrow 00:02:08.159$  reacting to cellular stress signals,

NOTE Confidence: 0.823722958564758

 $00:02:08.160 \rightarrow 00:02:11.496$  and among these are many that we know

NOTE Confidence: 0.823722958564758

 $00:02:11.496 \dashrightarrow 00:02:14.057$  are important in head neck cancer.

NOTE Confidence: 0.823722958564758

00:02:14.060 --> 00:02:15.752 So hypoxemia, DNA damage,

NOTE Confidence: 0.823722958564758

 $00:02:15.752 \longrightarrow 00:02:16.598$  replicative stress,

NOTE Confidence: 0.823722958564758

 $00{:}02{:}16.600 \dashrightarrow 00{:}02{:}19.547$  and ideally in response to these P.

NOTE Confidence: 0.823722958564758

 $00{:}02{:}19.550 \dashrightarrow 00{:}02{:}22.322$ 53 is activated and promotes the

NOTE Confidence: 0.823722958564758

 $00{:}02{:}22{.}322 \dashrightarrow 00{:}02{:}24.614$  transcription of target genes and

NOTE Confidence: 0.823722958564758

 $00{:}02{:}24.614 \dashrightarrow 00{:}02{:}26.804$  domains of cell cycle arrest DNA

 $00:02:26.804 \dashrightarrow 00:02:29.319$  repair a pop ptosis and others.

NOTE Confidence: 0.823722958564758

00:02:29.320 --> 00:02:29.824 However,

NOTE Confidence: 0.823722958564758

 $00:02:29.824 \rightarrow 00:02:33.352$  in head neck cancer were aware that

NOTE Confidence: 0.823722958564758

 $00:02:33.352 \longrightarrow 00:02:35.963$  P53 functionally disrupted in the

NOTE Confidence: 0.823722958564758

00:02:35.963 --> 00:02:39.491 majority in HPV associated head neck cancer.

NOTE Confidence: 0.823722958564758

00:02:39.500 - 00:02:42.769 P53 is wild type, but its degradation

NOTE Confidence: 0.823722958564758

 $00:02:42.769 \longrightarrow 00:02:45.610$  is fostered by viral proteins,

NOTE Confidence: 0.823722958564758

00:02:45.610 --> 00:02:49.768 an in HPV, negative head neck cancer.

NOTE Confidence: 0.823722958564758

00:02:49.770 --> 00:02:52.885 Over 85% have genomic disruption of P53,

NOTE Confidence: 0.823722958564758

 $00:02:52.890 \longrightarrow 00:02:54.674$  including in frame mutations,

NOTE Confidence: 0.823722958564758

 $00{:}02{:}54.674 \dashrightarrow 00{:}02{:}56.904$  truncating mutations and missense mutations,

NOTE Confidence: 0.823722958564758

 $00:02:56.910 \dashrightarrow 00:02:59.974$  and you can see here that many of

NOTE Confidence: 0.823722958564758

 $00{:}02{:}59{.}974 \dashrightarrow 00{:}03{:}03{.}150$  these are clustered in the DNA binding

NOTE Confidence: 0.823722958564758

 $00:03:03.150 \rightarrow 00:03:06.506$  domain and we know that this type

NOTE Confidence: 0.823722958564758

 $00{:}03{:}06{.}506 \dashrightarrow 00{:}03{:}09{.}810$  of mutation is Villa terius for the

NOTE Confidence: 0.823722958564758

 $00:03:09.810 \rightarrow 00:03:12.520$  Natural History of head neck cancer.

- NOTE Confidence: 0.823722958564758
- $00:03:12.520 \rightarrow 00:03:15.544$  So this figure comes from a large trial
- NOTE Confidence: 0.823722958564758
- 00:03:15.544 --> 00:03:18.310 that the legacy Kog Cooperative Group
- NOTE Confidence: 0.823722958564758
- $00{:}03{:}18{.}310 \dashrightarrow 00{:}03{:}21{.}910$  ran over 500 respected head neck cancers.
- NOTE Confidence: 0.823722958564758
- $00:03:21.910 \longrightarrow 00:03:23.438$  All respected to margin,
- NOTE Confidence: 0.823722958564758
- 00:03:23.438 --> 00:03:23.820 negativity,
- NOTE Confidence: 0.823722958564758
- $00:03:23.820 \longrightarrow 00:03:26.095$  and all offered appropriate risk
- NOTE Confidence: 0.823722958564758
- 00:03:26.095 --> 00:03:28.370 based animal therapy is with
- NOTE Confidence: 0.823722958564758
- $00{:}03{:}28{.}453 \dashrightarrow 00{:}03{:}31{.}077$  standard at the time and then P 50
- NOTE Confidence: 0.823722958564758
- $00{:}03{:}31{.}077 \dashrightarrow 00{:}03{:}33{.}427$  three was sequenced and you can
- NOTE Confidence: 0.823722958564758
- $00:03:33.427 \rightarrow 00:03:35.845$  see here that long term outcome.
- NOTE Confidence: 0.823722958564758
- 00:03:35.850 00:03:37.875 Was worse for those patients
- NOTE Confidence: 0.823722958564758
- $00{:}03{:}37.875 \dashrightarrow 00{:}03{:}39.495$  who had P53 mutation,
- NOTE Confidence: 0.823722958564758
- $00{:}03{:}39{.}500 \dashrightarrow 00{:}03{:}41{.}936$  and if you classified the mutations
- NOTE Confidence: 0.823722958564758
- 00:03:41.936 --> 00:03:43.560 as disruptive or nondisruptive,
- NOTE Confidence: 0.823722958564758
- $00:03:43.560 \longrightarrow 00:03:46.188$  it was worse for those with
- NOTE Confidence: 0.823722958564758

 $00{:}03{:}46.188 \dashrightarrow 00{:}03{:}48.472$  disruptive mutation and the definition

NOTE Confidence: 0.823722958564758

 $00{:}03{:}48.472 \dashrightarrow 00{:}03{:}51.136$  that was used in this paper.

NOTE Confidence: 0.823722958564758

 $00:03:51.140 \longrightarrow 00:03:53.654$  That was for disruptive was a

NOTE Confidence: 0.823722958564758

 $00:03:53.654 \rightarrow 00:03:55.856$  mutation that was either truncating

NOTE Confidence: 0.823722958564758

 $00:03:55.856 \longrightarrow 00:03:58.514$  or in the DNA binding domain.

NOTE Confidence: 0.823722958564758

 $00{:}03{:}58{.}520 \dashrightarrow 00{:}04{:}01{.}984$  So on the basis of these outcome data,

NOTE Confidence: 0.823722958564758

 $00:04:01.990 \dashrightarrow 00:04:04.594$  we were interested in the cognitive

NOTE Confidence: 0.823722958564758

00:04:04.594 --> 00:04:06.330 Akron Head Neck Committee,

NOTE Confidence: 0.823722958564758

 $00:04:06.330 \rightarrow 00:04:08.694$  which I chair in studying intensification

NOTE Confidence: 0.823722958564758

 $00{:}04{:}08{.}694 \dashrightarrow 00{:}04{:}11{.}300$  of the rapy for these poor prognosis

NOTE Confidence: 0.823722958564758

 $00{:}04{:}11{.}300 \dashrightarrow 00{:}04{:}13{.}705$  patients with disruptive P53 mutation.

NOTE Confidence: 0.823722958564758

 $00{:}04{:}13.710 \dashrightarrow 00{:}04{:}16.538$  But the first thing we wanted to

NOTE Confidence: 0.823722958564758

 $00:04:16.538 \longrightarrow 00:04:19.214$  do was examined how we really

NOTE Confidence: 0.823722958564758

 $00:04:19.214 \rightarrow 00:04:21.962$  should be calling the P53 mutation.

NOTE Confidence: 0.823722958564758

 $00{:}04{:}21{.}970 \dashrightarrow 00{:}04{:}24{.}483$  So we started with what we called

NOTE Confidence: 0.823722958564758

 $00:04:24.483 \rightarrow 00:04:25.560$  the poeta rule,

- NOTE Confidence: 0.823722958564758
- $00:04:25.560 \longrightarrow 00:04:27.800$  so those were the rules from the
- NOTE Confidence: 0.823722958564758
- 00:04:27.800 --> 00:04:30.234 paper I just showed you and we
- NOTE Confidence: 0.823722958564758
- $00:04:30.234 \rightarrow 00:04:32.807$  compared them to 14 other cloud 13
- NOTE Confidence: 0.823722958564758
- $00:04:32.807 \rightarrow 00:04:35.249$  other classifiers that are out there,
- NOTE Confidence: 0.823722958564758
- $00:04:35.250 \longrightarrow 00:04:37.483$  many of which are based on in
- NOTE Confidence: 0.823722958564758
- 00:04:37.483 --> 00:04:39.200 silico predictions of disruption,
- NOTE Confidence: 0.823722958564758
- $00{:}04{:}39{.}200 \dashrightarrow 00{:}04{:}41{.}755$  some of which are based on experimental
- NOTE Confidence: 0.823722958564758
- $00:04:41.755 \longrightarrow 00:04:44.007$  evidence actually of the decrease in
- NOTE Confidence: 0.823722958564758
- 00:04:44.007 --> 00:04:46.197 OIF 1 activation for every specific
- NOTE Confidence: 0.823722958564758
- $00{:}04{:}46.197 \dashrightarrow 00{:}04{:}48.627$  mutation and then we also examine Dar
- NOTE Confidence: 0.823722958564758
- $00:04:48.627 \rightarrow 00:04:50.336$  poeta rules augmented with information
- NOTE Confidence: 0.823722958564758
- $00{:}04{:}50{.}336 \dashrightarrow 00{:}04{:}52{.}166$  about the splice site mutations.
- NOTE Confidence: 0.823722958564758
- $00{:}04{:}52{.}170 \dashrightarrow 00{:}04{:}54{.}810$  And you can see that this very simple
- NOTE Confidence: 0.823722958564758
- $00{:}04{:}54{.}810$  -->  $00{:}04{:}56{.}826$  definition of truncating or DNA
- NOTE Confidence: 0.823722958564758
- 00:04:56.826 --> 00:04:58.538 binding domain actually outperformed
- NOTE Confidence: 0.823722958564758

 $00:04:58.538 \longrightarrow 00:05:01.120$  in terms of clinical prognosis.

NOTE Confidence: 0.823722958564758

 $00{:}05{:}01{.}120 \dashrightarrow 00{:}05{:}03{.}420$  All of the other indicators,

NOTE Confidence: 0.823722958564758

 $00:05:03.420 \longrightarrow 00:05:06.168$  and so in our clinical trial.

NOTE Confidence: 0.823722958564758

 $00:05:06.170 \longrightarrow 00:05:08.786$  We moved forward with this poeta

NOTE Confidence: 0.823722958564758

 $00{:}05{:}08.786 \dashrightarrow 00{:}05{:}11.085$  rules plus splice site mutations

NOTE Confidence: 0.823722958564758

 $00{:}05{:}11.085 \dashrightarrow 00{:}05{:}14.410$  and the trial that we're now about

NOTE Confidence: 0.823722958564758

 $00:05:14.410 \longrightarrow 00:05:15.360$  halfway through

NOTE Confidence: 0.807921290397644

 $00:05:15.446 \rightarrow 00:05:18.336$  is a randomized phase. Two trial of.

NOTE Confidence: 0.807921290397644

 $00:05:18.336 \rightarrow 00:05:20.246$  Post operative therapy for patients

NOTE Confidence: 0.807921290397644

 $00:05:20.246 \rightarrow 00:05:22.831$  who meet the criteria for radiation

NOTE Confidence: 0.807921290397644

 $00:05:22.831 \rightarrow 00:05:24.579$  but have negative margins,

NOTE Confidence: 0.807921290397644

 $00:05:24.580 \rightarrow 00:05:26.968$  don't meet the criteria for chemotherapy,

NOTE Confidence: 0.807921290397644

 $00{:}05{:}26{.}970 \dashrightarrow 00{:}05{:}29{.}594$  and then we want to ask in those

NOTE Confidence: 0.807921290397644

 $00:05:29.594 \rightarrow 00:05:31.760$  patients with disruptive mutation,

NOTE Confidence: 0.807921290397644

 $00:05:31.760 \longrightarrow 00:05:34.504$  do we see an advantage for the

NOTE Confidence: 0.807921290397644

 $00:05:34.504 \rightarrow 00:05:36.558$  addition of platinum that we

- NOTE Confidence: 0.807921290397644
- $00:05:36.558 \longrightarrow 00:05:38.538$  don't see in other patients?
- NOTE Confidence: 0.807921290397644
- $00:05:38.540 \longrightarrow 00:05:40.500$  This is supported by.
- NOTE Confidence: 0.807921290397644
- $00:05:40.500 \rightarrow 00:05:44.015$  Is Bisquick grant that takes care of
- NOTE Confidence: 0.807921290397644
- $00:05:44.015 \longrightarrow 00:05:47.382$  all of the sequencing and we have
- NOTE Confidence: 0.807921290397644
- $00{:}05{:}47{.}382 \dashrightarrow 00{:}05{:}49{.}864$  two investigators who are doing
- NOTE Confidence: 0.807921290397644
- $00:05:49.864 \rightarrow 00:05:52.714$  the mutation calling in real time.
- NOTE Confidence: 0.807921290397644
- $00:05:52.720 \longrightarrow 00:05:54.910$  So continue to support this trial
- NOTE Confidence: 0.807921290397644
- $00{:}05{:}54{.}910 \dashrightarrow 00{:}05{:}57{.}906$  and see this is kind of an important
- NOTE Confidence: 0.807921290397644
- $00{:}05{:}57{.}906 \dashrightarrow 00{:}06{:}00{.}596$  resource in terms of all the sequencing
- NOTE Confidence: 0.807921290397644
- 00:06:00.596 00:06:02.716 information that we're going to
- NOTE Confidence: 0.807921290397644
- $00:06:02.716 \rightarrow 00:06:06.628$  have on top of the clinical outcome.
- NOTE Confidence: 0.807921290397644
- 00:06:06.630 --> 00:06:09.563 We also have support for a clinical
- NOTE Confidence: 0.807921290397644
- $00:06:09.563 \rightarrow 00:06:11.891$  trials planning meeting at the NCI
- NOTE Confidence: 0.807921290397644
- $00{:}06{:}11.891 \dashrightarrow 00{:}06{:}14.222$  which is going to happen in January.
- NOTE Confidence: 0.807921290397644
- $00:06:14.230 \dashrightarrow 00:06:16.478$  The goal of this is to write trials
- NOTE Confidence: 0.807921290397644

 $00:06:16.478 \longrightarrow 00:06:18.709$  both for locally advanced and

NOTE Confidence: 0.807921290397644

00:06:18.709 --> 00:06:20.308 recurrent metastatic disease,

NOTE Confidence: 0.807921290397644

 $00:06:20.310 \rightarrow 00:06:21.450$  identifying promising therapies

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 $00{:}06{:}21.450 \dashrightarrow 00{:}06{:}22.970$  for P53 mutated cancer.

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 $00{:}06{:}22.970 \dashrightarrow 00{:}06{:}25.760$  We also want to develop a

NOTE Confidence: 0.807921290397644

 $00:06:25.760 \longrightarrow 00:06:26.690$  national infrastructure.

NOTE Confidence: 0.807921290397644

 $00:06:26.690 \rightarrow 00:06:28.550$  For the sequencing and mutation,

NOTE Confidence: 0.807921290397644

 $00{:}06{:}28.550 \dashrightarrow 00{:}06{:}30.460$  calling with the consensus approach

NOTE Confidence: 0.807921290397644

 $00{:}06{:}30{.}460 \dashrightarrow 00{:}06{:}33{.}153$  that all of the groups within the

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00:06:33.153 --> 00:06:35.289 NCT and will accept the breakout

NOTE Confidence: 0.807921290397644

 $00{:}06{:}35{.}289 \dashrightarrow 00{:}06{:}37{.}504$  groups for this have been meeting

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 $00:06:37.504 \longrightarrow 00:06:39.299$  for about five months now.

NOTE Confidence: 0.807921290397644

 $00:06:39.300 \longrightarrow 00:06:41.556$  I can tell you that the focus is

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 $00:06:41.556 \rightarrow 00:06:43.609$  very strong and immunotherapy and

NOTE Confidence: 0.807921290397644

 $00:06:43.609 \rightarrow 00:06:45.974$  synthetic lethal strategies and I'll.

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 $00:06:45.980 \longrightarrow 00:06:49.039$  I'll mention both of those in in

 $00:06:49.039 \rightarrow 00:06:51.490$  the remaining minutes of this talk.

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 $00{:}06{:}51{.}490 \dashrightarrow 00{:}06{:}54{.}090$  So head neck cancer is one of the

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 $00:06:54.090 \rightarrow 00:06:56.556$  cancers where it appears that increase

NOTE Confidence: 0.807921290397644

 $00:06:56.556 \rightarrow 00:06:58.736$  tumor mutation burden is predictive

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 $00{:}06{:}58.736 \dashrightarrow 00{:}07{:}01.038$  of response to immunotherapy.

NOTE Confidence: 0.807921290397644

 $00{:}07{:}01{.}040 \dashrightarrow 00{:}07{:}03{.}506$  And we know that this is a cancer with

NOTE Confidence: 0.807921290397644

00:07:03.506 --> 00:07:06.670 a higher number of nonsynonymous mutations,

NOTE Confidence: 0.807921290397644

 $00:07:06.670 \rightarrow 00:07:09.538$  particularly in the HPV negative cancers.

NOTE Confidence: 0.807921290397644

 $00:07:09.540 \dashrightarrow 00:07:12.096$  And in the platinum refractory setting,

NOTE Confidence: 0.807921290397644

 $00:07:12.100 \rightarrow 00:07:15.468$  both for Pember Lizum app in this early

NOTE Confidence: 0.807921290397644

 $00:07:15.468 \rightarrow 00:07:18.421$  single ARM trial and for development

NOTE Confidence: 0.807921290397644

 $00{:}07{:}18.421 \dashrightarrow 00{:}07{:}21.451$  in a randomized phase three trial.

NOTE Confidence: 0.807921290397644

 $00:07:21.460 \longrightarrow 00:07:24.202$  In the also in the platinum

NOTE Confidence: 0.807921290397644

00:07:24.202 --> 00:07:25.116 refractory setting,

NOTE Confidence: 0.807921290397644

 $00:07:25.120 \longrightarrow 00:07:28.214$  in both cases we see that as

00:07:28.214 --> 00:07:30.160 tumor mutation burden rises,

NOTE Confidence: 0.807921290397644

 $00:07:30.160 \longrightarrow 00:07:32.404$  the likelihood of benefit

NOTE Confidence: 0.807921290397644

 $00:07:32.404 \rightarrow 00:07:34.087$  from immunotherapy increases.

NOTE Confidence: 0.807921290397644

 $00:07:34.090 \rightarrow 00:07:36.436$  So working with my long term

NOTE Confidence: 0.807921290397644

00:07:36.436 --> 00:07:38.590 collaborator at Fox Chase Circle,

NOTE Confidence: 0.807921290397644

00:07:38.590 --> 00:07:39.030 Columbus,

NOTE Confidence: 0.807921290397644

 $00{:}07{:}39{.}030 \dashrightarrow 00{:}07{:}41.670$  we wanted to examine whether or

NOTE Confidence: 0.807921290397644

 $00:07:41.670 \longrightarrow 00:07:43.908$  not mutations in not only P.

NOTE Confidence: 0.807921290397644

 $00:07:43.910 \longrightarrow 00:07:44.295 53,$ 

NOTE Confidence: 0.807921290397644

 $00{:}07{:}44.295 \dashrightarrow 00{:}07{:}46.605$  which is the most common most

NOTE Confidence: 0.807921290397644

 $00{:}07{:}46.605 \dashrightarrow 00{:}07{:}48.276$  commonly mutated tumor suppressor

NOTE Confidence: 0.807921290397644

00:07:48.276 --> 00:07:50.036 and head neck cancer,

NOTE Confidence: 0.807921290397644

 $00{:}07{:}50{.}040 \dashrightarrow 00{:}07{:}52{.}756$  but also CDK into a which is

NOTE Confidence: 0.807921290397644

 $00:07:52.756 \longrightarrow 00:07:54.851$  mutated in slightly over half

NOTE Confidence: 0.807921290397644

 $00:07:54.851 \dashrightarrow 00:07:57.395$  of HPV negative cancers as well.

NOTE Confidence: 0.807921290397644

 $00:07:57.400 \longrightarrow 00:07:59.927$  See how these related to DNA damage

 $00{:}07{:}59{.}927 \dashrightarrow 00{:}08{:}01{.}967$  as reflected in tumor mutation

NOTE Confidence: 0.807921290397644

 $00:08:01.967 \longrightarrow 00:08:04.601$  burden with the idea of establishing

NOTE Confidence: 0.807921290397644

 $00{:}08{:}04{.}601 \dashrightarrow 00{:}08{:}07{.}258$  whether or not P53 mutated cancers.

NOTE Confidence: 0.807921290397644

 $00:08:07.260 \rightarrow 00:08:10.225$  Would be particularly susceptible or

NOTE Confidence: 0.807921290397644

 $00:08:10.225 \rightarrow 00:08:13.190$  appropriate for study with immunotherapy.

NOTE Confidence: 0.807921290397644

 $00:08:13.190 \longrightarrow 00:08:15.899$  We had access to a data set of 1010

NOTE Confidence: 0.807921290397644

 $00:08:15.899 \rightarrow 00:08:18.752$  HPV negative cancers that have been

NOTE Confidence: 0.807921290397644

 $00{:}08{:}18.752 \dashrightarrow 00{:}08{:}21.222$  profiled at Caris Life Sciences.

NOTE Confidence: 0.807921290397644

 $00:08:21.230 \longrightarrow 00:08:24.848$  There gene panel is about a 600 gene panel.

NOTE Confidence: 0.807921290397644

 $00:08:24.850 \rightarrow 00:08:26.945$  They exclude HPV associated cancers

NOTE Confidence: 0.807921290397644

 $00:08:26.945 \rightarrow 00:08:29.408$  with standard methods and then the

NOTE Confidence: 0.807921290397644

 $00{:}08{:}29{.}408 \dashrightarrow 00{:}08{:}31{.}840$  CDK into a mutations that we saw were

NOTE Confidence: 0.807921290397644

 $00:08:31.840 \rightarrow 00:08:34.498$  almost invariably truncations or deletions.

NOTE Confidence: 0.807921290397644

 $00{:}08{:}34{.}500 \dashrightarrow 00{:}08{:}36{.}906$  So we included all of those,

NOTE Confidence: 0.807921290397644

 $00{:}08{:}36{.}910 \dashrightarrow 00{:}08{:}40{.}046$  but for P53 we were interested once

 $00:08:40.046 \rightarrow 00:08:43.597$  again in what's the best way of calling?

NOTE Confidence: 0.807921290397644

 $00:08:43.600 \dashrightarrow 00:08:44.466$  Meaningful mutations,

NOTE Confidence: 0.807921290397644

 $00{:}08{:}44{.}466 \dashrightarrow 00{:}08{:}47{.}930$  so we started with the American College of

NOTE Confidence: 0.806212067604065

00:08:47.999 --> 00:08:49.919 Medical Genetics variants calling

NOTE Confidence: 0.806212067604065

 $00:08:49.919 \longrightarrow 00:08:52.319$  this included essentially all the

NOTE Confidence: 0.806212067604065

 $00:08:52.319 \longrightarrow 00:08:54.698$  P53 mutations that that we SPA.

NOTE Confidence: 0.806212067604065

 $00{:}08{:}54.700 \dashrightarrow 00{:}08{:}56.968$  We then looked for consensus between

NOTE Confidence: 0.806212067604065

 $00:08:56.968 \rightarrow 00:09:00.800$  the ACM G and two other variant calling

NOTE Confidence: 0.806212067604065

 $00:09:00.800 \rightarrow 00:09:02.244$  algorithms, interference linver.

NOTE Confidence: 0.806212067604065

 $00:09:02.244 \rightarrow 00:09:05.338$  We use the International Agency for Research

NOTE Confidence: 0.806212067604065

 $00{:}09{:}05{.}338 \dashrightarrow 00{:}09{:}08{.}458$  on Cancer guidelines for what was dominant,

NOTE Confidence: 0.806212067604065

 $00:09:08.460 \longrightarrow 00:09:11.380$  negative or loss of function.

NOTE Confidence: 0.806212067604065

 $00{:}09{:}11{.}380 \dashrightarrow 00{:}09{:}14{.}396$  We then looked at the variance is defined

NOTE Confidence: 0.806212067604065

 $00:09:14.396 \rightarrow 00:09:17.974$  by the poeta rules that I just alluded to,

NOTE Confidence: 0.806212067604065

 $00:09:17.980 \longrightarrow 00:09:20.756$  and then we called out those patients who

NOTE Confidence: 0.806212067604065

 $00:09:20.756 \rightarrow 00:09:23.799$  seem to have gain of function mutations,

 $00:09:23.800 \rightarrow 00:09:25.858$  most of which are defined experimentally

NOTE Confidence: 0.806212067604065

00:09:25.858 --> 00:09:28.060 across a range of publications,

NOTE Confidence: 0.806212067604065

 $00{:}09{:}28.060 \dashrightarrow 00{:}09{:}29.461$  and TMB was.

NOTE Confidence: 0.806212067604065

00:09:29.461 --> 00:09:32.263 Measured just by counting all nonsynonymous

NOTE Confidence: 0.806212067604065

 $00{:}09{:}32.263 \dashrightarrow 00{:}09{:}34.927$  missense mutations across the about 1.4

NOTE Confidence: 0.806212067604065

 $00:09:34.927 \dashrightarrow 00:09:38.128$  mega bases that are included in this panel.

NOTE Confidence: 0.806212067604065

00:09:38.130 - > 00:09:40.764 This shows you the the patient

NOTE Confidence: 0.806212067604065

 $00:09:40.764 \longrightarrow 00:09:42.081$  characteristics so predominantly

NOTE Confidence: 0.806212067604065

 $00:09:42.081 \rightarrow 00:09:43.619$  oral cavity in order.

NOTE Confidence: 0.806212067604065

 $00:09:43.620 \dashrightarrow 00:09:47.004$  Pharynx cancers as we see in the clinic.

NOTE Confidence: 0.806212067604065

00:09:47.010 --> 00:09:48.366 Males outnumbering females,

NOTE Confidence: 0.806212067604065

 $00:09:48.366 \longrightarrow 00:09:51.530$  and as you see at the bottom,

NOTE Confidence: 0.806212067604065

 $00{:}09{:}51{.}530 \dashrightarrow 00{:}09{:}54{.}533$  the number of patients who had P53

NOTE Confidence: 0.806212067604065

 $00{:}09{:}54{.}533 \dashrightarrow 00{:}09{:}57{.}245$  mutation by the karris was higher

NOTE Confidence: 0.806212067604065

 $00{:}09{:}57{.}245 \dashrightarrow 00{:}10{:}00{.}367$  than if we looked at the consensus

 $00:10:00.456 \rightarrow 00:10:03.697$  calls or the disruptive call gain of

NOTE Confidence: 0.806212067604065

 $00:10:03.697 \longrightarrow 00:10:07.485$  function was less than 10% of all of

NOTE Confidence: 0.806212067604065

 $00:10:07.485 \longrightarrow 00:10:10.968$  the mutations that we saw in be 53,

NOTE Confidence: 0.806212067604065

 $00:10:10.970 \dashrightarrow 00:10:14.578$  and indeed it turned out that either P.

NOTE Confidence: 0.806212067604065

 $00{:}10{:}14.580 \dashrightarrow 00{:}10{:}17.340$ 53 or CDK into a mutation.

NOTE Confidence: 0.806212067604065

 $00{:}10{:}17{.}340 \dashrightarrow 00{:}10{:}20{.}175$  Was associated with an increase in TMB.

NOTE Confidence: 0.806212067604065

 $00{:}10{:}20{.}180 \dashrightarrow 00{:}10{:}22{.}371$  Here we looked for threshold of 15

NOTE Confidence: 0.806212067604065

 $00:10:22.371 \rightarrow 00:10:25.374$  per per per megabases as being likely

NOTE Confidence: 0.806212067604065

 $00:10:25.374 \rightarrow 00:10:27.869$  predictive of response to immunotherapy.

NOTE Confidence: 0.806212067604065

 $00{:}10{:}27.870 \dashrightarrow 00{:}10{:}30.814$  And you can see that across the board

NOTE Confidence: 0.806212067604065

 $00{:}10{:}30{.}814 \dashrightarrow 00{:}10{:}33{.}432$  having both genes mutated was associated

NOTE Confidence: 0.806212067604065

 $00:10:33.432 \rightarrow 00:10:37.188$  with higher TMB than having one or the other,

NOTE Confidence: 0.806212067604065

 $00{:}10{:}37{.}190 \dashrightarrow 00{:}10{:}40{.}011$  and The only exception here was that

NOTE Confidence: 0.806212067604065

 $00:10:40.011 \rightarrow 00:10:42.356$  those patients with gain of function

NOTE Confidence: 0.806212067604065

 $00{:}10{:}42.356 \dashrightarrow 00{:}10{:}44.827$  mutations in P53 did not have an

NOTE Confidence: 0.806212067604065

 $00{:}10{:}44{.}900 \dashrightarrow 00{:}10{:}47{.}350$  increase in tumor mutation burden.

- NOTE Confidence: 0.806212067604065
- 00:10:47.350 --> 00:10:48.322 So you know,
- NOTE Confidence: 0.806212067604065
- $00:10:48.322 \longrightarrow 00:10:50.266$  we concluded that mutation of P53
- NOTE Confidence: 0.806212067604065
- $00{:}10{:}50{.}266 \dashrightarrow 00{:}10{:}53{.}210$  or CDK in two ways associated with
- NOTE Confidence: 0.806212067604065
- $00:10:53.210 \longrightarrow 00:10:54.906$  increased tumor mutation burden.
- NOTE Confidence: 0.806212067604065
- $00:10:54.910 \rightarrow 00:10:57.676$  This is highest when they're damaging
- NOTE Confidence: 0.806212067604065
- $00:10:57.676 \longrightarrow 00:11:00.804$  mutations in both jeans and so just to
- NOTE Confidence: 0.806212067604065
- 00:11:00.804 --> 00:11:03.979 kind of segue to the next part of the talk,
- NOTE Confidence: 0.806212067604065
- $00{:}11{:}03{.}980 \dashrightarrow 00{:}11{:}06{.}412$  where I'm going to talk a little bit
- NOTE Confidence: 0.806212067604065
- $00{:}11{:}06{.}412 \dashrightarrow 00{:}11{:}08{.}899$  more about synthetic lethal strategies.
- NOTE Confidence: 0.806212067604065
- 00:11:08.900 --> 00:11:11.544 P53 mutated head neck cancer, I think,
- NOTE Confidence: 0.806212067604065
- 00:11:11.544 --> 00:11:14.183 remains a really important subject for study,
- NOTE Confidence: 0.806212067604065
- 00:11:14.190 --> 00:11:15.555 because it's common.
- NOTE Confidence: 0.806212067604065
- $00{:}11{:}15{.}555 \dashrightarrow 00{:}11{:}17{.}830$  It has a poor prognosis.
- NOTE Confidence: 0.806212067604065
- 00:11:17.830 --> 00:11:19.087 We still don't,
- NOTE Confidence: 0.806212067604065
- $00:11:19.087 \rightarrow 00:11:22.020$  after many decades of people examining this,
- NOTE Confidence: 0.806212067604065

 $00:11:22.020 \rightarrow 00:11:24.946$  have agents which directly target mutated P.

NOTE Confidence: 0.806212067604065

 $00:11:24.950 \longrightarrow 00:11:25.479$  53.

NOTE Confidence: 0.806212067604065

 $00:11:25.479 \rightarrow 00:11:28.653$  And so the increasing evidence that

NOTE Confidence: 0.806212067604065

 $00:11:28.653 \rightarrow 00:11:31.131$  synthetic lethal strategies might have

NOTE Confidence: 0.806212067604065

 $00:11:31.131 \longrightarrow 00:11:33.952$  promise in these patients is has kind

NOTE Confidence: 0.806212067604065

 $00{:}11{:}33{.}952 \dashrightarrow 00{:}11{:}37{.}439$  of attracted our attention in the lab.

NOTE Confidence: 0.806212067604065

 $00{:}11{:}37{.}440 \dashrightarrow 00{:}11{:}40{.}536$  And so one of the things that we

NOTE Confidence: 0.806212067604065

00:11:40.536 --> 00:11:42.900 know about disruptive P53 mutation

NOTE Confidence: 0.806212067604065

 $00:11:42.900 \rightarrow 00:11:45.900$  is that you lose the cell,

NOTE Confidence: 0.806212067604065

 $00:11:45.900 \rightarrow 00:11:48.522$  loses the ability to perform cell

NOTE Confidence: 0.806212067604065

00:11:48.522 - 00:11:51.679 cycle arrest at the G1 S transition,

NOTE Confidence: 0.806212067604065

 $00{:}11{:}51{.}680 \dashrightarrow 00{:}11{:}55{.}008$  and as a result it becomes much more

NOTE Confidence: 0.806212067604065

 $00{:}11{:}55{.}008 \dashrightarrow 00{:}11{:}58{.}224$  dependent on transition at G2 M and so

NOTE Confidence: 0.806212067604065

 $00{:}11{:}58{.}224 \dashrightarrow 00{:}12{:}01{.}397$  we I mean obviously many people have

NOTE Confidence: 0.806212067604065

 $00:12:01.397 \rightarrow 00:12:05.023$  been interested in this across many cancers,

NOTE Confidence: 0.806212067604065

 $00{:}12{:}05{.}030 \dashrightarrow 00{:}12{:}07{.}270$  but we were interested in

- NOTE Confidence: 0.806212067604065
- $00:12:07.270 \longrightarrow 00:12:09.062$  examining some of the.
- NOTE Confidence: 0.806212067604065
- $00{:}12{:}09{.}070 \dashrightarrow 00{:}12{:}10{.}690$  Potential targets that regulate G2
- NOTE Confidence: 0.806212067604065
- $00{:}12{:}10.690 \dashrightarrow 00{:}12{:}13.000$  M We know that auroras increasing.
- NOTE Confidence: 0.806212067604065
- $00:12:13.000 \rightarrow 00:12:15.848$  I'll show you a little bit about this.
- NOTE Confidence: 0.806212067604065
- $00{:}12{:}15.850 \dashrightarrow 00{:}12{:}17.990$  We know that Aurora expression
- NOTE Confidence: 0.806212067604065
- 00:12:17.990 --> 00:12:20.130 is increased in head neck
- NOTE Confidence: 0.819094598293304
- $00{:}12{:}20{.}209 \dashrightarrow 00{:}12{:}22{.}414$  cancer and. Aurora content
- NOTE Confidence: 0.819094598293304
- $00:12:22.414 \longrightarrow 00:12:27.870$  will go up at the end of G2.
- NOTE Confidence: 0.819094598293304
- $00{:}12{:}27.870 \dashrightarrow 00{:}12{:}32.238$  Its activity is required to localize
- NOTE Confidence: 0.819094598293304
- $00{:}12{:}32{.}238 \dashrightarrow 00{:}12{:}38{.}726$  CDK one to the to the centromere to to.
- NOTE Confidence: 0.819094598293304
- 00:12:38.730 --> 00:12:41.710 Foster mitotic entry Aurora also,
- NOTE Confidence: 0.819094598293304
- $00{:}12{:}41.710 \dashrightarrow 00{:}12{:}44.685$  in addition to its roles
- NOTE Confidence: 0.819094598293304
- $00{:}12{:}44.685 \dashrightarrow 00{:}12{:}46.470$  in centrosome maturation.
- NOTE Confidence: 0.819094598293304
- $00{:}12{:}46{.}470 \dashrightarrow 00{:}12{:}50{.}856$  It also has the property of.
- NOTE Confidence: 0.819094598293304
- $00:12:50.860 \longrightarrow 00:12:52.354$  Activating the city.
- NOTE Confidence: 0.819094598293304

00:12:52.354 --> 00:12:53.848 See 25 phosphatase,

NOTE Confidence: 0.819094598293304

 $00:12:53.850 \rightarrow 00:12:56.430$  which removes an inhibitory phosphorylation

NOTE Confidence: 0.819094598293304

 $00:12:56.430 \longrightarrow 00:13:00.319$  from CDK one and on the other hand,

NOTE Confidence: 0.819094598293304

 $00:13:00.320 \longrightarrow 00:13:03.872$  it's important to know that that

NOTE Confidence: 0.819094598293304

 $00:13:03.872 \longrightarrow 00:13:05.648$  inhibitory phosphorylation is

NOTE Confidence: 0.819094598293304

 $00{:}13{:}05{.}648 \dashrightarrow 00{:}13{:}08{.}114$  placed by the mitotic checkpoint

NOTE Confidence: 0.819094598293304

 $00{:}13{:}08{.}114 \dashrightarrow 00{:}13{:}11{.}318$  kin ase we want and so both we

NOTE Confidence: 0.819094598293304

 $00:13:11.318 \rightarrow 00:13:13.940$  won an Auror recognized is up

NOTE Confidence: 0.819094598293304

 $00:13:13.940 \rightarrow 00:13:16.428$  regulated and head neck cancer.

NOTE Confidence: 0.819094598293304

 $00:13:16.428 \rightarrow 00:13:19.348$  Both of them are potential.

NOTE Confidence: 0.819094598293304

 $00:13:19.350 \longrightarrow 00:13:21.230$  Points of synthetic lethality

NOTE Confidence: 0.819094598293304

 $00:13:21.230 \longrightarrow 00:13:23.110$  in P53 mutated cancers,

NOTE Confidence: 0.819094598293304

 $00:13:23.110 \longrightarrow 00:13:26.330$  but they appear to have kind of

NOTE Confidence: 0.819094598293304

00:13:26.330 --> 00:13:28.280 contradictory or opposing roles,

NOTE Confidence: 0.819094598293304

 $00:13:28.280 \rightarrow 00:13:31.584$  and so that the data that I'm going

NOTE Confidence: 0.819094598293304

 $00:13:31.584 \rightarrow 00:13:34.865$  to show you now will try to make

- NOTE Confidence: 0.819094598293304
- 00:13:34.865 00:13:38.377 the case that by Co treating these
- NOTE Confidence: 0.819094598293304
- 00:13:38.377 --> 00:13:41.437 cancers with an Aurora inhibitor,
- NOTE Confidence: 0.819094598293304
- $00{:}13{:}41{.}440 \dashrightarrow 00{:}13{:}43{.}416$  which will lead to.
- NOTE Confidence: 0.819094598293304
- 00:13:43.416 --> 00:13:44.898 Abnormal spindle formation.
- NOTE Confidence: 0.819094598293304
- 00:13:44.900 --> 00:13:45.988 Defective cytokinesis,
- NOTE Confidence: 0.819094598293304
- $00:13:45.988 \rightarrow 00:13:49.252$  but by inhibiting the rural will
- NOTE Confidence: 0.819094598293304
- $00:13:49.252 \rightarrow 00:13:52.633$  lose the ability to remove the
- NOTE Confidence: 0.819094598293304
- $00:13:52.633 \rightarrow 00:13:54.289$  inhibitory phosphorylation from
- NOTE Confidence: 0.819094598293304
- $00{:}13{:}54{.}289 \dashrightarrow 00{:}13{:}57{.}699$  CDK one and that will result in
- NOTE Confidence: 0.819094598293304
- $00:13:57.699 \rightarrow 00:14:00.195$  cell cycle arrest that we can
- NOTE Confidence: 0.819094598293304
- $00:14:00.200 \longrightarrow 00:14:02.670$  counter that by inhibition of
- NOTE Confidence: 0.819094598293304
- $00:14:02.670 \longrightarrow 00:14:05.140$  we won so that phosphorylation
- NOTE Confidence: 0.819094598293304
- $00{:}14{:}05{.}229 \dashrightarrow 00{:}14{:}07{.}864$  isn't placed and accelerate these
- NOTE Confidence: 0.819094598293304
- $00{:}14{:}07.864 \dashrightarrow 00{:}14{:}10.499$  cells into mitosis where given
- NOTE Confidence: 0.819094598293304
- $00:14:10.587 \rightarrow 00:14:13.347$  the spindle disruption that's been
- NOTE Confidence: 0.819094598293304

 $00:14:13.347 \rightarrow 00:14:16.107$  caused by the Aurora inhibition.

NOTE Confidence: 0.819094598293304

 $00:14:16.110 \rightarrow 00:14:19.078$  They will be unable to complete a normal

NOTE Confidence: 0.819094598293304

 $00{:}14{:}19.078 \dashrightarrow 00{:}14{:}21.552$  mitosis and instead will apoptose

NOTE Confidence: 0.819094598293304

 $00{:}14{:}21.552 \dashrightarrow 00{:}14{:}23.756$  are undergo mitotic catastrophe.

NOTE Confidence: 0.819094598293304

 $00:14:23.760 \longrightarrow 00:14:24.227$  So,

NOTE Confidence: 0.819094598293304

00:14:24.227 --> 00:14:24.694 um,

NOTE Confidence: 0.819094598293304

 $00:14:24.694 \rightarrow 00:14:27.496$  it's been recognized that Aurora content

NOTE Confidence: 0.819094598293304

 $00:14:27.496 \longrightarrow 00:14:30.397$  is increased in the face of loss of

NOTE Confidence: 0.819094598293304

 $00:14:30.397 \longrightarrow 00:14:32.959$  P53 and their host of publications,

NOTE Confidence: 0.819094598293304

 $00{:}14{:}32{.}960 \dashrightarrow 00{:}14{:}34{.}945$  which demonstrate that increased Aurora

NOTE Confidence: 0.819094598293304

 $00{:}14{:}34{.}945 \dashrightarrow 00{:}14{:}37{.}550$  levels are correlated with poor prognosis.

NOTE Confidence: 0.819094598293304

 $00:14:37.550 \longrightarrow 00:14:40.546$  I'll show you some of our work.

NOTE Confidence: 0.819094598293304

 $00:14:40.550 \longrightarrow 00:14:43.133$  This is a panel of cell lines

NOTE Confidence: 0.819094598293304

 $00:14:43.133 \rightarrow 00:14:45.647$  that that we use in the lab,

NOTE Confidence: 0.819094598293304

 $00{:}14{:}45{.}650 \dashrightarrow 00{:}14{:}47{.}470$  all of which have either

NOTE Confidence: 0.819094598293304

 $00:14:47.470 \longrightarrow 00:14:49.290$  mutated or P53 null status,

- NOTE Confidence: 0.819094598293304
- $00:14:49.290 \longrightarrow 00:14:51.482$  and you can see that all of them
- NOTE Confidence: 0.819094598293304
- $00{:}14{:}51{.}482 \dashrightarrow 00{:}14{:}53{.}408$  increase the expression of arorae
- NOTE Confidence: 0.819094598293304
- $00:14:53.408 \longrightarrow 00:14:55.160$  relative to either fibroblasts
- NOTE Confidence: 0.819094598293304
- $00:14:55.160 \longrightarrow 00:14:56.970$  or normal epithelial tissue.
- NOTE Confidence: 0.819094598293304
- 00:14:56.970 00:14:59.966 And when I was at Fox Chase,
- NOTE Confidence: 0.819094598293304
- $00{:}14{:}59{.}970 \dashrightarrow 00{:}15{:}03{.}130$  we worked on a Aqua essay and insight
- NOTE Confidence: 0.819094598293304
- $00:15:03.130 \longrightarrow 00:15:05.819$  to fluorescence as say for Aurora that
- NOTE Confidence: 0.819094598293304
- $00:15:05.819 \rightarrow 00:15:08.549$  could be applied to tissue microarrays.
- NOTE Confidence: 0.819094598293304
- $00{:}15{:}08{.}550 \dashrightarrow 00{:}15{:}11{.}438$  And so you see here that green is
- NOTE Confidence: 0.819094598293304
- $00:15:11.438 \rightarrow 00:15:14.111$  for carrot and defines where these
- NOTE Confidence: 0.819094598293304
- $00{:}15{:}14{.}111 \dashrightarrow 00{:}15{:}16{.}913$  head neck cancer nests are within
- NOTE Confidence: 0.819094598293304
- $00:15:17.002 \dashrightarrow 00:15:19.708$  the tissue core Blues for dampit.
- NOTE Confidence: 0.819094598293304
- $00{:}15{:}19{.}710 \dashrightarrow 00{:}15{:}23{.}148$  So that will be your nucleus and red is
- NOTE Confidence: 0.819094598293304
- $00{:}15{:}23.148 \dashrightarrow 00{:}15{:}27.008$  for Aurora and in this Aurora high cancer.
- NOTE Confidence: 0.819094598293304
- $00{:}15{:}27.010 \dashrightarrow 00{:}15{:}28.840$  What you can particularly appreciate
- NOTE Confidence: 0.819094598293304

 $00:15:28.840 \longrightarrow 00:15:31.167$  is the high level of expression

NOTE Confidence: 0.819094598293304

 $00:15:31.167 \longrightarrow 00:15:33.307$  of Aurora within the nucleus.

NOTE Confidence: 0.819094598293304

 $00{:}15{:}33{.}310 \dashrightarrow 00{:}15{:}35{.}452$  When we looked at nuclear Aurora

NOTE Confidence: 0.819094598293304

 $00:15:35.452 \rightarrow 00:15:37.285$  in the tissue microarray first

NOTE Confidence: 0.819094598293304

 $00:15:37.285 \longrightarrow 00:15:39.651$  for all cases we saw that high

NOTE Confidence: 0.819094598293304

 $00{:}15{:}39{.}651 \dashrightarrow 00{:}15{:}41{.}273$  Aurora expression was associated

NOTE Confidence: 0.819094598293304

 $00:15:41.273 \longrightarrow 00:15:42.590$  with worse survival.

NOTE Confidence: 0.819094598293304

 $00:15:42.590 \longrightarrow 00:15:43.902$  This is also true,

NOTE Confidence: 0.819094598293304

00:15:43.902 --> 00:15:45.870 just is a reflection of Natural

NOTE Confidence: 0.819094598293304

 $00:15:45.943 \rightarrow 00:15:48.109$  History in those patients who had

NOTE Confidence: 0.819094598293304

 $00:15:48.109 \longrightarrow 00:15:50.072$  had no post operative treatments

NOTE Confidence: 0.819094598293304

 $00:15:50.072 \rightarrow 00:15:51.860$  and never been exposed.

NOTE Confidence: 0.819094598293304

 $00{:}15{:}51{.}860 \dashrightarrow 00{:}15{:}54{.}184$  Any DNA damaging agents and we were

NOTE Confidence: 0.819094598293304

 $00:15:54.184 \rightarrow 00:15:56.866$  able to show that this was entirely

NOTE Confidence: 0.819094598293304

 $00:15:56.866 \rightarrow 00:15:59.278$  driven by the HPV negative cancers.

NOTE Confidence: 0.819094598293304

 $00:15:59.280 \longrightarrow 00:16:01.576$  So on the basis of this these

- NOTE Confidence: 0.819094598293304
- $00:16:01.576 \longrightarrow 00:16:03.739$  data we went to Millennium.
- NOTE Confidence: 0.819094598293304
- $00:16:03.740 \longrightarrow 00:16:05.246$  And argued that.
- NOTE Confidence: 0.819094598293304
- $00:16:05.246 \rightarrow 00:16:08.258$  Aurora could potentially be a good
- NOTE Confidence: 0.819094598293304
- $00:16:08.258 \rightarrow 00:16:10.926$  target in head and neck cancer.
- NOTE Confidence: 0.790267467498779
- $00:16:10.930 \rightarrow 00:16:14.074$  They were doing a trial of Al assertive,
- NOTE Confidence: 0.790267467498779
- $00{:}16{:}14.080 \dashrightarrow 00{:}16{:}17.140$  which is in Aurora a inhibitor.
- NOTE Confidence: 0.790267467498779
- $00:16:17.140 \rightarrow 00:16:18.740$  Val asserted monotherapy across
- NOTE Confidence: 0.790267467498779
- 00:16:18.740 --> 00:16:20.740 a bunch of solid tumors,
- NOTE Confidence: 0.790267467498779
- $00:16:20.740 \longrightarrow 00:16:22.924$  and we were able to convince
- NOTE Confidence: 0.790267467498779
- $00:16:22.924 \rightarrow 00:16:25.940$  them to add a head neck cohort,
- NOTE Confidence: 0.790267467498779
- $00:16:25.940 \rightarrow 00:16:28.250$  but this was crushingly disappointing
- NOTE Confidence: 0.790267467498779
- $00{:}16{:}28.250 \dashrightarrow 00{:}16{:}31.022$  because the response rate for Aurora
- NOTE Confidence: 0.790267467498779
- $00:16:31.022 \longrightarrow 00:16:33.338$  monotherapy in in head and neck
- NOTE Confidence: 0.790267467498779
- $00{:}16{:}33{.}338 \dashrightarrow 00{:}16{:}35{.}930$  cancer turned out to be about 9% and
- NOTE Confidence: 0.790267467498779
- $00:16:35.930 \rightarrow 00:16:37.490$  given the increasing experimental
- NOTE Confidence: 0.790267467498779

 $00:16:37.490 \rightarrow 00:16:39.909$  evidence that are or inhibition may

NOTE Confidence: 0.790267467498779

 $00:16:39.909 \rightarrow 00:16:41.537$  always be intrinsically limited.

NOTE Confidence: 0.790267467498779

00:16:41.540 --> 00:16:43.940 Limited by this kind of compens

NOTE Confidence: 0.790267467498779

 $00:16:43.940 \longrightarrow 00:16:45.540$  atory cell cycle arrest.

NOTE Confidence: 0.790267467498779

 $00{:}16{:}45{.}540 \dashrightarrow 00{:}16{:}48{.}764$  We were then interested in what would be.

NOTE Confidence: 0.790267467498779

 $00{:}16{:}48.770 \dashrightarrow 00{:}16{:}51.750$  The rational combination with

NOTE Confidence: 0.790267467498779

 $00:16:51.750 \longrightarrow 00:16:54.730$  Arorae inhibition that could.

NOTE Confidence: 0.790267467498779

 $00:16:54.730 \rightarrow 00:16:57.268$  Optimize the targeting of what we

NOTE Confidence: 0.790267467498779

 $00{:}16{:}57{.}268 \dashrightarrow 00{:}17{:}00{.}276$  continued to think was likely to be

NOTE Confidence: 0.790267467498779

 $00{:}17{:}00{.}276 \dashrightarrow 00{:}17{:}02{.}742$  an important target in this disease,

NOTE Confidence: 0.790267467498779

 $00{:}17{:}02.750 \dashrightarrow 00{:}17{:}05.550$  and so any Mendez and colleagues at the

NOTE Confidence: 0.790267467498779

 $00:17:05.550 \rightarrow 00:17:07.693$  University of Washington together with

NOTE Confidence: 0.790267467498779

 $00{:}17{:}07{.}693 \dashrightarrow 00{:}17{:}09{.}973$  Dell Yarbrough are former colleague

NOTE Confidence: 0.790267467498779

 $00{:}17{:}09{.}973 \dashrightarrow 00{:}17{:}12{.}880$  here had undertaken a functional kind,

NOTE Confidence: 0.790267467498779

00:17:12.880 --> 00:17:13.680 ohmic screen.

NOTE Confidence: 0.790267467498779

 $00:17:13.680 \longrightarrow 00:17:14.480$  In P53,

- NOTE Confidence: 0.790267467498779
- $00{:}17{:}14.480 \dashrightarrow 00{:}17{:}16.880$  mutated head and neck cancer and
- NOTE Confidence: 0.790267467498779
- $00{:}17{:}16.956 \dashrightarrow 00{:}17{:}19.917$  actually Aurora came out of that screen.
- NOTE Confidence: 0.790267467498779
- $00{:}17{:}19{.}920 \dashrightarrow 00{:}17{:}22{.}302$  But another thing that came out
- NOTE Confidence: 0.790267467498779
- $00{:}17{:}22{.}302 \dashrightarrow 00{:}17{:}24{.}296$  was this mitotic checkpoint kinase
- NOTE Confidence: 0.790267467498779
- $00{:}17{:}24.296 \dashrightarrow 00{:}17{:}25.976$  that I just alluded to.
- NOTE Confidence: 0.790267467498779
- $00:17:25.980 \longrightarrow 00:17:27.078$  We want and.
- NOTE Confidence: 0.790267467498779
- $00{:}17{:}27.078 \dashrightarrow 00{:}17{:}28.908$  People have been interested in
- NOTE Confidence: 0.790267467498779
- $00:17:28.908 \longrightarrow 00:17:31.403$  the idea that inhibitors of G1
- NOTE Confidence: 0.790267467498779
- $00:17:31.403 \rightarrow 00:17:33.513$  will abrogate the G2 checkpoint.
- NOTE Confidence: 0.790267467498779
- $00:17:33.520 \longrightarrow 00:17:34.258$  You have.
- NOTE Confidence: 0.790267467498779
- $00{:}17{:}34.258 \dashrightarrow 00{:}17{:}36.103$  The G1 checkpoint is already
- NOTE Confidence: 0.790267467498779
- $00{:}17{:}36{.}103 \dashrightarrow 00{:}17{:}38{.}567$  advocated by P53 mutation and that
- NOTE Confidence: 0.790267467498779
- $00{:}17{:}38{.}567 \dashrightarrow 00{:}17{:}40{.}707$  this might accelerate cell death,
- NOTE Confidence: 0.790267467498779
- $00{:}17{:}40.710 \dashrightarrow 00{:}17{:}42.978$  particularly in the presence of DNA
- NOTE Confidence: 0.790267467498779
- 00:17:42.978 --> 00:17:45.866 damage such as you might generate with
- NOTE Confidence: 0.790267467498779

 $00:17:45.866 \rightarrow 00:17:48.470$  cisplatin and they showed in animal

NOTE Confidence: 0.790267467498779

 $00{:}17{:}48.470 \dashrightarrow 00{:}17{:}51.078$  models that we one inhibitor MK 1775,

NOTE Confidence: 0.790267467498779

00:17:51.080 --> 00:17:54.264 which is now known as the data sorted,

NOTE Confidence: 0.790267467498779

 $00{:}17{:}54{.}270 \dashrightarrow 00{:}17{:}56{.}375$  was synergistic with platinum in

NOTE Confidence: 0.790267467498779

 $00{:}17{:}56.375 \dashrightarrow 00{:}17{:}59.040$  P53 mutated head neck cancer models.

NOTE Confidence: 0.790267467498779

 $00:17:59.040 \longrightarrow 00:18:01.315$  Eddie Mendez then took this forward as NOTE Confidence: 0.790267467498779

00:18:01.315 -> 00:18:03.647 a window trial and head neck cancer,

NOTE Confidence: 0.790267467498779

 $00:18:03.650 \rightarrow 00:18:05.834$  so a small number of patients treated

NOTE Confidence: 0.790267467498779

 $00{:}18{:}05{.}834 \dashrightarrow 00{:}18{:}08{.}311$  with a DAB assertive together with

NOTE Confidence: 0.790267467498779

00:18:08.311 - > 00:18:10.279 low dose weekly chemotherapy.

NOTE Confidence: 0.790267467498779

 $00{:}18{:}10{.}280 \dashrightarrow 00{:}18{:}13{.}152$  And you can see here that the majority

NOTE Confidence: 0.790267467498779

 $00{:}18{:}13{.}152 \dashrightarrow 00{:}18{:}15{.}354$  of patients had some diminution in

NOTE Confidence: 0.790267467498779

 $00{:}18{:}15{.}354 \dashrightarrow 00{:}18{:}18{.}569$  tumor size and a number of them had

NOTE Confidence: 0.790267467498779

 $00:18:18.569 \rightarrow 00:18:20.629$  rather major pathologic responses,

NOTE Confidence: 0.790267467498779

 $00:18:20.630 \longrightarrow 00:18:21.752$  and most intriguingly,

NOTE Confidence: 0.790267467498779

 $00{:}18{:}21.752 \dashrightarrow 00{:}18{:}24.370$  you can see that there was evidence

- NOTE Confidence: 0.790267467498779
- $00:18:24.443 \rightarrow 00:18:25.799$  of target engagement,
- NOTE Confidence: 0.790267467498779
- $00{:}18{:}25{.}800 \dashrightarrow 00{:}18{:}28{.}188$  and so among those patients who
- NOTE Confidence: 0.790267467498779
- $00:18:28.188 \longrightarrow 00:18:28.984$  had responses,
- NOTE Confidence: 0.790267467498779
- 00:18:28.990 --> 00:18:31.425 there was a decrease in
- NOTE Confidence: 0.790267467498779
- $00:18:31.425 \longrightarrow 00:18:32.886$  phosphorylation of CDK.
- NOTE Confidence: 0.790267467498779
- $00{:}18{:}32{.}890 \dashrightarrow 00{:}18{:}35{.}900$  There was a decrease in
- NOTE Confidence: 0.790267467498779
- $00:18:35.900 \longrightarrow 00:18:38.910$  fast focus Stone Age 3.
- NOTE Confidence: 0.790267467498779
- 00:18:38.910 --> 00:18:41.640 And potentially you could see
- NOTE Confidence: 0.790267467498779
- 00:18:41.640 --> 00:18:44.954 some increase in gamma, H2, ax.
- NOTE Confidence: 0.790267467498779
- $00:18:44.954 \rightarrow 00:18:48.326$  They also were able to correlate
- NOTE Confidence: 0.790267467498779
- 00:18:48.326 --> 00:18:50.715 both pathologic and clinical
- NOTE Confidence: 0.790267467498779
- $00{:}18{:}50{.}715 \dashrightarrow 00{:}18{:}54{.}207$  response with the presence of P53
- NOTE Confidence: 0.790267467498779
- $00{:}18{:}54{.}207 \dashrightarrow 00{:}18{:}57{.}781$  mutation in the HPV negative cancers
- NOTE Confidence: 0.790267467498779
- $00{:}18{:}57{.}781 \dashrightarrow 00{:}19{:}00{.}089$  and across the board.
- NOTE Confidence: 0.790267467498779
- $00{:}19{:}00{.}090 \dashrightarrow 00{:}19{:}02{.}722$  These P53 mutations are
- NOTE Confidence: 0.790267467498779

00:19:02.722 --> 00:19:04.696 disruptive or deletions.

NOTE Confidence: 0.790267467498779

 $00{:}19{:}04.700 \dashrightarrow 00{:}19{:}07.166$  So we've been exploring whether or

NOTE Confidence: 0.790267467498779

 $00:19:07.166 \rightarrow 00:19:10.530$  not you can combine Aurora A and we

NOTE Confidence: 0.790267467498779

 $00:19:10.530 \rightarrow 00:19:12.585$  want inhibition and observe synergy

NOTE Confidence: 0.790267467498779

00:19:12.585 --> 00:19:15.278 in P53 mutated head neck cancer,

NOTE Confidence: 0.790267467498779

 $00:19:15.280 \rightarrow 00:19:19.078$  and you see here a picture of John Wooley,

NOTE Confidence: 0.790267467498779

 $00:19:19.080 \rightarrow 00:19:21.200$  my colleague in the lamp,

NOTE Confidence: 0.790267467498779

 $00:19:21.200 \rightarrow 00:19:24.154$  who has done the majority of these

NOTE Confidence: 0.790267467498779

00:19:24.154 --> 00:19:26.698 experiments and so you'll see MLN,

NOTE Confidence: 0.790267467498779

 $00:19:26.700 \rightarrow 00:19:28.500$  that's the Aurora inhibitor,

NOTE Confidence: 0.790267467498779

 $00{:}19{:}28{.}500 \dashrightarrow 00{:}19{:}31{.}200$  Azd 1775 that's the wee one

NOTE Confidence: 0.790267467498779

00:19:31.280 --> 00:19:33.610 inhibitor and we see synergy.

NOTE Confidence: 0.790267467498779

00:19:33.610 --> 00:19:36.130 In terms of cell viability,

NOTE Confidence: 0.790267467498779

 $00:19:36.130 \rightarrow 00:19:38.565$  soft auger oncosphere formation and

NOTE Confidence: 0.790267467498779

 $00{:}19{:}38{.}565 \dashrightarrow 00{:}19{:}41{.}569$  this was present in two separate

NOTE Confidence: 0.790267467498779

 $00:19:41.569 \rightarrow 00:19:44.491$  HPV negative head neck cancer cell

- NOTE Confidence: 0.790267467498779
- $00:19:44.491 \longrightarrow 00:19:47.190$  lines that bear P53 mutations.
- NOTE Confidence: 0.790267467498779
- 00:19:47.190 --> 00:19:49.914 Trying to figure out whether or
- NOTE Confidence: 0.790267467498779
- 00:19:49.914 --> 00:19:51.730 not our our guests
- NOTE Confidence: 0.809300720691681
- $00{:}19{:}51{.}829 \dashrightarrow 00{:}19{:}54{.}739$  about the mechanism was correct.
- NOTE Confidence: 0.809300720691681
- $00:19:54.740 \longrightarrow 00:19:59.474$  You can see here that when you give the.
- NOTE Confidence: 0.809300720691681
- $00{:}19{:}59{.}480 \dashrightarrow 00{:}20{:}01{.}675$  Aurora inhibitor there's a dramatic
- NOTE Confidence: 0.809300720691681
- $00:20:01.675 \rightarrow 00:20:04.190$  increase in phosphorylation of CDK one.
- NOTE Confidence: 0.809300720691681
- $00:20:04.190 \rightarrow 00:20:06.734$  This happens in a slightly different
- NOTE Confidence: 0.809300720691681
- $00{:}20{:}06{.}734 \dashrightarrow 00{:}20{:}09{.}349$  timeline in the two South and
- NOTE Confidence: 0.809300720691681
- $00:20:09.349 \longrightarrow 00:20:11.454$  the two different cell lines,
- NOTE Confidence: 0.809300720691681
- $00:20:11.460 \rightarrow 00:20:14.456$  but seems to be a reproducible phenomenon,
- NOTE Confidence: 0.809300720691681
- $00{:}20{:}14.460 \dashrightarrow 00{:}20{:}16.698$  and that's abrogated by the addition
- NOTE Confidence: 0.809300720691681
- $00:20:16.698 \rightarrow 00:20:19.689$  of the wee one inhibitor and completely
- NOTE Confidence: 0.809300720691681
- $00{:}20{:}19.689 \dashrightarrow 00{:}20{:}23.014$  abolished when you gives it to together.
- NOTE Confidence: 0.809300720691681
- $00{:}20{:}23.020 \dashrightarrow 00{:}20{:}26.452$  This results in an increase in the number
- NOTE Confidence: 0.809300720691681

 $00:20:26.452 \longrightarrow 00:20:29.959$  of mitotic figures that's abnormal to the.

NOTE Confidence: 0.809300720691681

 $00{:}20{:}29{.}960 \dashrightarrow 00{:}20{:}32{.}546$  The. Presence of of really only

NOTE Confidence: 0.809300720691681

 $00:20:32.546 \rightarrow 00:20:34.801$  single digit normal mitotic figures

NOTE Confidence: 0.809300720691681

 $00:20:34.801 \rightarrow 00:20:37.495$  in the presence of the combination.

NOTE Confidence: 0.809300720691681

00:20:37.500 --> 00:20:40.034 So if you just walk through here,

NOTE Confidence: 0.809300720691681

 $00{:}20{:}40.040 \dashrightarrow 00{:}20{:}42.206$  these are the normal mitotic figures.

NOTE Confidence: 0.809300720691681

00:20:42.210 - 00:20:44.737 When you give the wee one inhibitor,

NOTE Confidence: 0.809300720691681

 $00:20:44.740 \longrightarrow 00:20:47.110$  you get some dis aggregation of

NOTE Confidence: 0.809300720691681

 $00{:}20{:}47.110 \dashrightarrow 00{:}20{:}49.063$  chromatin reflected here in the

NOTE Confidence: 0.809300720691681

00:20:49.063 -> 00:20:50.899 fast food Stone Age 3 stain.

NOTE Confidence: 0.809300720691681

 $00:20:50.900 \rightarrow 00:20:53.066$  When you give the Aurora inhibitor,

NOTE Confidence: 0.809300720691681

 $00:20:53.070 \rightarrow 00:20:55.492$  you get the formation of these multipolar

NOTE Confidence: 0.809300720691681

 $00:20:55.492 \longrightarrow 00:20:57.409$  spindles three to four spindles,

NOTE Confidence: 0.809300720691681

00:20:57.410 - > 00:20:59.660 Purcell, and when you give the

NOTE Confidence: 0.809300720691681

 $00:20:59.660 \longrightarrow 00:21:02.288$  two together you get a, uh.

NOTE Confidence: 0.809300720691681

00:21:02.288 --> 00:21:05.880 Abnormal catastrophic mitotic figure.

- NOTE Confidence: 0.809300720691681
- $00{:}21{:}05{.}880 \dashrightarrow 00{:}21{:}09{.}380$  We also showed in using Annexin 5
- NOTE Confidence: 0.809300720691681
- $00{:}21{:}09{.}380 \dashrightarrow 00{:}21{:}12{.}985$  flow and looking for cleaved PARP that
- NOTE Confidence: 0.809300720691681
- $00{:}21{:}12{.}985 \dashrightarrow 00{:}21{:}16{.}790$  there's an increase in a pop ptosis.
- NOTE Confidence: 0.809300720691681
- $00:21:16.790 \longrightarrow 00:21:19.562$  And we wanted to compare this
- NOTE Confidence: 0.809300720691681
- 00:21:19.562 --> 00:21:21.410 to Aurora B inhibition,
- NOTE Confidence: 0.809300720691681
- $00:21:21.410 \longrightarrow 00:21:24.890$  which completely cuts off mitotic entry
- NOTE Confidence: 0.809300720691681
- $00:21:24.890 \longrightarrow 00:21:27.210$  by aggregating the phosphorylation
- NOTE Confidence: 0.809300720691681
- $00{:}21{:}27{.}296 \dashrightarrow 00{:}21{:}30{.}152$  of histone H3 and there was no
- NOTE Confidence: 0.809300720691681
- $00{:}21{:}30{.}152 \dashrightarrow 00{:}21{:}32{.}182$  synergy between these two agents
- NOTE Confidence: 0.809300720691681
- $00:21:32.182 \longrightarrow 00:21:34.360$  and and you can see there.
- NOTE Confidence: 0.809300720691681
- 00:21:34.360 --> 00:21:37.948 The lack of fastball, histone H3,
- NOTE Confidence: 0.809300720691681
- 00:21:37.950 --> 00:21:41.740 an increase in DNA damage.
- NOTE Confidence: 0.809300720691681
- $00{:}21{:}41.740 \dashrightarrow 00{:}21{:}44.820$  Taking this into xenograft models here at
- NOTE Confidence: 0.809300720691681
- $00{:}21{:}44.820 \dashrightarrow 00{:}21{:}48.698$  either of two doses of the wee one inhibitor,
- NOTE Confidence: 0.809300720691681
- $00{:}21{:}48.700 \dashrightarrow 00{:}21{:}51.244$  the standard dose of the Aurora
- NOTE Confidence: 0.809300720691681

 $00:21:51.244 \rightarrow 00:21:53.455$  inhibitor tumors continued to grow

NOTE Confidence: 0.809300720691681

 $00:21:53.455 \longrightarrow 00:21:55.655$  not too differently from vehicle,

NOTE Confidence: 0.809300720691681

00:21:55.660 -> 00:21:58.705 but when we gave the two together,

NOTE Confidence: 0.809300720691681

 $00:21:58.710 \longrightarrow 00:22:02.091$  there was control of tumor growth and

NOTE Confidence: 0.809300720691681

 $00:22:02.091 \rightarrow 00:22:03.540$  actually statistically significant

NOTE Confidence: 0.809300720691681

 $00{:}22{:}03.607 \dashrightarrow 00{:}22{:}06.289$  improvement in survival for the animals.

NOTE Confidence: 0.809300720691681

 $00:22:06.290 \rightarrow 00:22:08.964$  Looking at the tumors under the microscope

NOTE Confidence: 0.809300720691681

 $00:22:08.964 \rightarrow 00:22:11.857$  when we gave the two agents together,

NOTE Confidence: 0.809300720691681

 $00{:}22{:}11.860 \dashrightarrow 00{:}22{:}14.326$  there was a decrease in proliferation

NOTE Confidence: 0.809300720691681

00:22:14.326 --> 00:22:16.240 reflected in decreased Ki 67,

NOTE Confidence: 0.809300720691681

 $00:22:16.240 \longrightarrow 00:22:18.844$  there was increased cleaved caspase and

NOTE Confidence: 0.809300720691681

00:22:18.844 --> 00:22:21.809 there was a decrease in fast for CDK,

NOTE Confidence: 0.809300720691681

 $00{:}22{:}21.810 \dashrightarrow 00{:}22{:}24.428$  one within tissue and if we did

NOTE Confidence: 0.809300720691681

00:22:24.428 --> 00:22:26.469 Aquaphor phospho CDK one and

NOTE Confidence: 0.809300720691681

 $00:22:26.469 \rightarrow 00:22:28.574$  counted the amount of phosphorus,

NOTE Confidence: 0.809300720691681

 $00:22:28.580 \rightarrow 00:22:31.756$  IDK one signal in the tumor leading edge.

 $00:22:31.760 \rightarrow 00:22:35.330$  You can see this was dramatically decreased.

NOTE Confidence: 0.809300720691681

 $00:22:35.330 \longrightarrow 00:22:37.568$  Ellisor to has been a difficult

NOTE Confidence: 0.809300720691681

 $00:22:37.568 \rightarrow 00:22:39.939$  drug to work within the clinic.

NOTE Confidence: 0.809300720691681

 $00:22:39.940 \rightarrow 00:22:41.860$  It's associated with Mila suppression,

NOTE Confidence: 0.809300720691681

 $00:22:41.860 \longrightarrow 00:22:43.775$  and there's been a negative

NOTE Confidence: 0.809300720691681

00:22:43.775 -> 00:22:45.307 phase three monotherapy trial,

NOTE Confidence: 0.809300720691681

 $00:22:45.310 \longrightarrow 00:22:46.120$  and lymphoma,

NOTE Confidence: 0.809300720691681

 $00:22:46.120 \longrightarrow 00:22:49.360$  and so we were concerned that the development

NOTE Confidence: 0.809300720691681

 $00:22:49.434 \longrightarrow 00:22:51.835$  of that agent might not go forward.

NOTE Confidence: 0.809300720691681

00:22:51.840 --> 00:22:52.199 However,

NOTE Confidence: 0.809300720691681

 $00{:}22{:}52{.}199 \dashrightarrow 00{:}22{:}54{.}712$  there's been a number of 2nd generation

NOTE Confidence: 0.809300720691681

 $00{:}22{:}54{.}712 \dashrightarrow 00{:}22{:}57{.}018$  or or inhibitors that have come

NOTE Confidence: 0.809300720691681

 $00{:}22{:}57.018 \dashrightarrow 00{:}22{:}59.764$  forward and we've had access to a

NOTE Confidence: 0.809300720691681

 $00{:}22{:}59{.}764 \dashrightarrow 00{:}23{:}02{.}158$  compound from Taiho called task 119

NOTE Confidence: 0.809300720691681

 $00{:}23{:}02{.}158 \dashrightarrow 00{:}23{:}04{.}506$  recently been acquired by Bit Track.
00:23:04.506 --> 00:23:07.180 And it's gonna be called Vic 1911

NOTE Confidence: 0.809300720691681

 $00{:}23{:}07{.}265 \dashrightarrow 00{:}23{:}10{.}170$  moving forward and once again across a

NOTE Confidence: 0.809300720691681

 $00{:}23{:}10.170 \dashrightarrow 00{:}23{:}13.691$  range of P53 mutated cell lines we see

NOTE Confidence: 0.809300720691681

 $00:23:13.691 \rightarrow 00:23:16.347$  dramatic synergy for the two agents.

NOTE Confidence: 0.809300720691681

00:23:16.347 --> 00:23:17.261 Once again,

NOTE Confidence: 0.809300720691681

 $00:23:17.261 \rightarrow 00:23:20.003$  we see synergy in xenograft models.

NOTE Confidence: 0.809300720691681

 $00{:}23{:}20.010 \dashrightarrow 00{:}23{:}23.465$  This is confocal microscopy that

NOTE Confidence: 0.809300720691681

 $00:23:23.465 \rightarrow 00:23:26.920$  again shows you the multipolar

NOTE Confidence: 0.809300720691681

00:23:27.030 --> 00:23:30.252 spindle formation with the use of

NOTE Confidence: 0.809300720691681

 $00{:}23{:}30{.}252 \dashrightarrow 00{:}23{:}32{.}400$  task 119 is the

NOTE Confidence: 0.815518438816071

 $00{:}23{:}32{.}515 \dashrightarrow 00{:}23{:}34{.}379$  Aurora inhibitor.

NOTE Confidence: 0.815518438816071

 $00{:}23{:}34{.}380 \dashrightarrow 00{:}23{:}37{.}089$  But with the cells really arresting in

NOTE Confidence: 0.815518438816071

 $00{:}23{:}37.089 \dashrightarrow 00{:}23{:}39.847$  that or becoming quiet sent in that

NOTE Confidence: 0.815518438816071

 $00{:}23{:}39{.}847 \dashrightarrow 00{:}23{:}42{.}127$  multipolar spindle state an as they

NOTE Confidence: 0.815518438816071

 $00:23:42.204 \rightarrow 00:23:44.766$  then attempt to enter mitosis in the

NOTE Confidence: 0.815518438816071

 $00:23:44.766 \longrightarrow 00:23:47.785$  in the presence of both the wee one

00:23:47.785 --> 00:23:49.700 inhibitor and the Aurora inhibitor,

NOTE Confidence: 0.815518438816071

 $00:23:49.700 \longrightarrow 00:23:51.232$  developing these very catastrophic

NOTE Confidence: 0.815518438816071

 $00:23:51.232 \rightarrow 00:23:53.116$  mitotic phenotypes, an notice that

NOTE Confidence: 0.815518438816071

00:23:53.116 --> 00:23:56.210 I'm sort of running out of time here,

NOTE Confidence: 0.815518438816071

 $00:23:56.210 \rightarrow 00:23:58.884$  so I won't March you through this,

NOTE Confidence: 0.815518438816071

 $00{:}23{:}58.890 \dashrightarrow 00{:}24{:}01.954$  but the mechanism looks to be identical here,

NOTE Confidence: 0.815518438816071

 $00:24:01.960 \longrightarrow 00:24:04.840$  as what we saw with assertive.

NOTE Confidence: 0.815518438816071

 $00{:}24{:}04{.}840 \dashrightarrow 00{:}24{:}06{.}630$  I'm working with our Columbus

NOTE Confidence: 0.815518438816071

 $00{:}24{:}06{.}630 \dashrightarrow 00{:}24{:}08{.}420$  is Lambert at Fox Chase.

NOTE Confidence: 0.815518438816071

 $00{:}24{:}08{.}420 \dashrightarrow 00{:}24{:}10{.}200$  We undertook a high throughput

NOTE Confidence: 0.815518438816071

00:24:10.200 --> 00:24:12.970 screen to see if we could find

NOTE Confidence: 0.815518438816071

 $00{:}24{:}12.970 \dashrightarrow 00{:}24{:}15.260$  additional partners that would be.

NOTE Confidence: 0.815518438816071

 $00{:}24{:}15{.}260 \dashrightarrow 00{:}24{:}17{.}888$  Both hindering and an fostering mitotic

NOTE Confidence: 0.815518438816071

00:24:17.888 --> 00:24:21.119 entry again with the attempt to exploit

NOTE Confidence: 0.815518438816071

 $00{:}24{:}21{.}119 \dashrightarrow 00{:}24{:}23{.}449$  these multiple regulators of G2,

 $00:24:23.450 \longrightarrow 00:24:25.772$  M and another hit that appeared

NOTE Confidence: 0.815518438816071

00:24:25.772 --> 00:24:28.548 very strong was the check one

NOTE Confidence: 0.815518438816071

 $00{:}24{:}28{.}548 \dashrightarrow 00{:}24{:}30{.}276$  inhibitor Prexasertib agent.

NOTE Confidence: 0.815518438816071

 $00:24:30.280 \longrightarrow 00:24:32.890$  It's not really moving forward in

NOTE Confidence: 0.815518438816071

 $00:24:32.890 \longrightarrow 00:24:35.739$  the clinic because of its toxicity,

NOTE Confidence: 0.815518438816071

 $00:24:35.740 \longrightarrow 00:24:39.058$  but I wanted to show this just

NOTE Confidence: 0.815518438816071

 $00:24:39.058 \rightarrow 00:24:42.079$  because with very low dose Ng and

NOTE Confidence: 0.815518438816071

 $00:24:42.079 \rightarrow 00:24:45.320$  a single dose we saw a profound.

NOTE Confidence: 0.815518438816071

 $00{:}24{:}45{.}320 \dashrightarrow 00{:}24{:}47{.}042$  Energetic survival effects that make us

NOTE Confidence: 0.815518438816071

 $00:24:47.042 \rightarrow 00:24:49.308$  hopeful that with a number of these pairs,

NOTE Confidence: 0.815518438816071

 $00:24:49.310 \longrightarrow 00:24:51.886$  we might be able to go to very

NOTE Confidence: 0.815518438816071

 $00{:}24{:}51{.}886 \dashrightarrow 00{:}24{:}53{.}740$  low doses in the clinic.

NOTE Confidence: 0.815518438816071

 $00:24:53.740 \longrightarrow 00:24:56.050$  So test 119 has completed

NOTE Confidence: 0.815518438816071

 $00:24:56.050 \rightarrow 00:24:57.436$  two clinical trials.

NOTE Confidence: 0.815518438816071

 $00{:}24{:}57{.}440 \dashrightarrow 00{:}25{:}00{.}206$  There's a recommended phase two dose.

NOTE Confidence: 0.815518438816071

 $00:25:00.210 \rightarrow 00:25:03.290$  The toxicity seems to be very manageable

 $00:25:03.290 \dashrightarrow 00:25:05.750$  with diarrhea and eye disorders.

NOTE Confidence: 0.815518438816071

 $00{:}25{:}05{.}750 \dashrightarrow 00{:}25{:}07{.}598$  Probably the prominent most

NOTE Confidence: 0.815518438816071

00:25:07.598 --> 00:25:08.984 prominent side effects,

NOTE Confidence: 0.815518438816071

 $00:25:08.990 \longrightarrow 00:25:11.834$  and so we are moving forward

NOTE Confidence: 0.815518438816071

 $00:25:11.834 \rightarrow 00:25:14.530$  with a window trial in HPV,

NOTE Confidence: 0.815518438816071

 $00{:}25{:}14.530 \dashrightarrow 00{:}25{:}17.080$  negative head neck cancer that will

NOTE Confidence: 0.815518438816071

 $00{:}25{:}17.080 \dashrightarrow 00{:}25{:}20.070$  have both an initial dose escalation.

NOTE Confidence: 0.815518438816071

 $00:25:20.070 \longrightarrow 00:25:22.054$  Looking at the combination

NOTE Confidence: 0.815518438816071

 $00{:}25{:}22.054 \dashrightarrow 00{:}25{:}24.534$  of Vic and DAB assertive.

NOTE Confidence: 0.815518438816071

 $00{:}25{:}24{.}540 \dashrightarrow 00{:}25{:}26{.}948$  And followed by a dose expansion and

NOTE Confidence: 0.815518438816071

00:25:26.948 --> 00:25:29.485 that will be part of Project two of

NOTE Confidence: 0.815518438816071

 $00{:}25{:}29{.}485 \dashrightarrow 00{:}25{:}32{.}459$  our head next 4 so I wanted to leave

NOTE Confidence: 0.815518438816071

 $00{:}25{:}32{.}459 \dashrightarrow 00{:}25{:}34{.}649$  a couple of minutes for questions,

NOTE Confidence: 0.815518438816071

 $00{:}25{:}34.650 \dashrightarrow 00{:}25{:}36.785$  but I didn't want to end without

NOTE Confidence: 0.815518438816071

 $00:25:36.785 \longrightarrow 00:25:39.291$  first of all calling out all of

 $00:25:39.291 \rightarrow 00:25:41.191$  the fabulous colleagues who were

NOTE Confidence: 0.815518438816071

 $00{:}25{:}41{.}191 \dashrightarrow 00{:}25{:}43{.}511$  part of the team that they put

NOTE Confidence: 0.815518438816071

00:25:43.511 --> 00:25:45.741 the head and explore in and then

NOTE Confidence: 0.815518438816071

 $00:25:45.741 \rightarrow 00:25:47.376$  acknowledging all the people whose

NOTE Confidence: 0.815518438816071

 $00:25:47.376 \longrightarrow 00:25:49.139$  work I've just talked about,

NOTE Confidence: 0.815518438816071

00:25:49.140 --> 00:25:51.005 particularly John Wooley Jannike Parameshwar

NOTE Confidence: 0.815518438816071

 $00{:}25{:}51{.}005 \dashrightarrow 00{:}25{:}53{.}520$  on in Teresa Sandoval Schaefer in the lamp.

NOTE Confidence: 0.815518438816071

 $00:25:53.520 \longrightarrow 00:25:55.220$  So thank you very much.

NOTE Confidence: 0.815518438816071

00:25:55.220 --> 00:25:55.610 Barbara,

NOTE Confidence: 0.815518438816071

 $00:25:55.610 \rightarrow 00:25:56.390$  thank you.

NOTE Confidence: 0.834983050823212

 $00:25:56.390 \longrightarrow 00:25:57.707$  That's fabulous work.

NOTE Confidence: 0.834983050823212

 $00{:}25{:}57.707 \dashrightarrow 00{:}26{:}00{.}341$  Congratulations on all of it and

NOTE Confidence: 0.834983050823212

 $00{:}26{:}00{.}341 \dashrightarrow 00{:}26{:}02{.}713$  and folks can submit questions on

NOTE Confidence: 0.834983050823212

 $00:26:02.713 \rightarrow 00:26:05.780$  the on the chat box of the zoom,

NOTE Confidence: 0.834983050823212

 $00:26:05.780 \longrightarrow 00:26:08.524$  but I wanted to ask, you know,

NOTE Confidence: 0.834983050823212

 $00:26:08.524 \rightarrow 00:26:10.906$  with regard as you look through

- NOTE Confidence: 0.834983050823212
- $00:26:10.906 \longrightarrow 00:26:12.895$  the combination of an Aurora
- NOTE Confidence: 0.834983050823212
- $00:26:12.895 \longrightarrow 00:26:14.765$  kinase and we want inhibitors,
- NOTE Confidence: 0.834983050823212
- $00:26:14.770 \rightarrow 00:26:18.680$  do you have a sense of 1st what might emerge?
- NOTE Confidence: 0.834983050823212
- $00:26:18.680 \rightarrow 00:26:21.020$  I'm even when you're getting response
- NOTE Confidence: 0.834983050823212
- $00:26:21.020 \rightarrow 00:26:23.758$  because of the complexity of those pathways.
- NOTE Confidence: 0.834983050823212
- $00:26:23.760 \longrightarrow 00:26:25.436$  What might emerges mechanism?
- NOTE Confidence: 0.834983050823212
- $00{:}26{:}25{.}436 \dashrightarrow 00{:}26{:}27{.}531$  Resistance that will occur when
- NOTE Confidence: 0.834983050823212
- $00:26:27.531 \longrightarrow 00:26:30.186$  you have dual inhibition of any and
- NOTE Confidence: 0.834983050823212
- $00{:}26{:}30{.}186 \dashrightarrow 00{:}26{:}32{.}552$  then the second question I have is
- NOTE Confidence: 0.834983050823212
- $00:26:32.552 \rightarrow 00:26:34.540$  what do you anticipate will be the
- NOTE Confidence: 0.834983050823212
- $00:26:34.540 \rightarrow 00:26:36.300$  toxicity profile or the therapeutic
- NOTE Confidence: 0.834983050823212
- $00:26:36.300 \rightarrow 00:26:38.060$  the rapeutic window for the combination
- NOTE Confidence: 0.827964603900909
- $00:26:38.060 \rightarrow 00:26:40.496$  clinically. So the we want inhibitors
- NOTE Confidence: 0.827964603900909
- 00:26:40.496 --> 00:26:42.527 been quite tolerable 'cause I'm
- NOTE Confidence: 0.827964603900909
- $00{:}26{:}42.527 \dashrightarrow 00{:}26{:}44.585$  going to take the second question
- NOTE Confidence: 0.827964603900909

00:26:44.585 --> 00:26:46.269 first 'cause I've already wrestled

NOTE Confidence: 0.827964603900909

 $00{:}26{:}46{.}269 \dashrightarrow 00{:}26{:}48{.}613$  with X and a lot that we want.

NOTE Confidence: 0.827964603900909

 $00:26:48.620 \rightarrow 00:26:49.928$  Inhibitors been quite tolerable

NOTE Confidence: 0.827964603900909

 $00:26:49.928 \longrightarrow 00:26:52.339$  in the clinic but when it was

NOTE Confidence: 0.827964603900909

 $00:26:52.339 \rightarrow 00:26:53.899$  combined with PARP inhibition,

NOTE Confidence: 0.827964603900909

 $00:26:53.900 \rightarrow 00:26:56.036$  diarrhea really became the dose limiting.

NOTE Confidence: 0.827964603900909

 $00{:}26{:}56{.}040 \dashrightarrow 00{:}26{:}58{.}860$  Side effect, and so this second

NOTE Confidence: 0.827964603900909

 $00:26:58.860 \rightarrow 00:27:01.123$  generation Aurora inhibitor did have

NOTE Confidence: 0.827964603900909

 $00{:}27{:}01{.}123 \dashrightarrow 00{:}27{:}04{.}140$  about a 25% rate of high grade diarrhea

NOTE Confidence: 0.827964603900909

 $00{:}27{:}04.140 \dashrightarrow 00{:}27{:}06.720$  at the recommended phase two dose.

NOTE Confidence: 0.827964603900909

 $00:27:06.720 \longrightarrow 00:27:09.810$  So the two things that were

NOTE Confidence: 0.827964603900909

 $00:27:09.810 \longrightarrow 00:27:12.220$  sort of hoping is 1.

NOTE Confidence: 0.827964603900909

 $00:27:12.220 \rightarrow 00:27:15.271$  That will get away with lower doses as we

NOTE Confidence: 0.827964603900909

 $00:27:15.271 \rightarrow 00:27:18.570$  have in the animal models and second of all,

NOTE Confidence: 0.827964603900909

 $00:27:18.570 \longrightarrow 00:27:20.772$  the diarrhea as it dose limiting

NOTE Confidence: 0.827964603900909

 $00:27:20.772 \longrightarrow 00:27:23.640$  toxicity is one of the easier ones to

 $00{:}27{:}23.640 \dashrightarrow 00{:}27{:}26.737$  manage and so that if we're on top of

NOTE Confidence: 0.827964603900909

 $00:27:26.737 \rightarrow 00:27:29.152$  this with an Imodium regimen early on,

NOTE Confidence: 0.827964603900909

 $00:27:29.160 \longrightarrow 00:27:31.778$  hopefully that will be helpful in terms

NOTE Confidence: 0.827964603900909

 $00{:}27{:}31.778 \dashrightarrow 00{:}27{:}33.591$  of resistance mechanisms with this

NOTE Confidence: 0.827964603900909

 $00:27:33.591 \rightarrow 00:27:35.481$  is not something that we've really

NOTE Confidence: 0.827964603900909

 $00{:}27{:}35{.}481 \dashrightarrow 00{:}27{:}37{.}638$  gone into with the combination yet,

NOTE Confidence: 0.827964603900909

 $00{:}27{:}37{.}640 \dashrightarrow 00{:}27{:}40{.}720$  but is well studied for both of the

NOTE Confidence: 0.827964603900909

 $00:27:40.720 \longrightarrow 00:27:42.587$  agents independently and one of the.

NOTE Confidence: 0.827964603900909

 $00{:}27{:}42.590 \dashrightarrow 00{:}27{:}44.605$  Resistance mechanisms to the Aurora

NOTE Confidence: 0.827964603900909

 $00{:}27{:}44.605 \dashrightarrow 00{:}27{:}47.758$  agents has been a kind of conformational

NOTE Confidence: 0.827964603900909

00:27:47.758 --> 00:27:49.890 dependence on the inhibitor,

NOTE Confidence: 0.827964603900909

 $00{:}27{:}49{.}890 \dashrightarrow 00{:}27{:}52{.}512$  so inhibitor binds to the activated

NOTE Confidence: 0.827964603900909

 $00{:}27{:}52{.}512 \dashrightarrow 00{:}27{:}56{.}274$  form of Aurora A and if you get a

NOTE Confidence: 0.827964603900909

 $00{:}27{:}56{.}274 \dashrightarrow 00{:}27{:}58{.}868$  an adaptive process where the cell

NOTE Confidence: 0.827964603900909

00:27:58.868 --> 00:28:01.738 just generates more inactive Aurora,

 $00:28:01.740 \longrightarrow 00:28:04.698$  the current generation of inhibitors may

NOTE Confidence: 0.827964603900909

 $00:28:04.698 \rightarrow 00:28:08.577$  not work as well and there is a group.

NOTE Confidence: 0.827964603900909

00:28:08.580 --> 00:28:11.298 Kevan Shokat lab has been developing

NOTE Confidence: 0.827964603900909

 $00:28:11.298 \rightarrow 00:28:13.600$  novel Aurora inhibitors that maybe.

NOTE Confidence: 0.827964603900909

 $00{:}28{:}13.600 \dashrightarrow 00{:}28{:}16.528$  More able to bind the inactive

NOTE Confidence: 0.827964603900909

 $00{:}28{:}16{.}528 \dashrightarrow 00{:}28{:}21{.}144$  confirmation as well. And in terms

NOTE Confidence: 0.827964603900909

 $00{:}28{:}21{.}144 \dashrightarrow 00{:}28{:}28{.}480$  of we want inhibitors there there is.

NOTE Confidence: 0.827964603900909

 $00:28:28.480 \longrightarrow 00:28:35.900$  Suggestions that? The the.

NOTE Confidence: 0.827964603900909

00:28:35.900 --> 00:28:40.760 Do you need damage effects of?

NOTE Confidence: 0.827964603900909

 $00:28:40.760 \rightarrow 00:28:45.350$  That we want inhibitors may have an S phase.

NOTE Confidence: 0.827964603900909

00:28:45.350 --> 00:28:48.675 Could actually upregulate some checkpoints

NOTE Confidence: 0.827964603900909

 $00:28:48.675 \rightarrow 00:28:53.220$  that are earlier in the cell cycle.

NOTE Confidence: 0.827964603900909

 $00:28:53.220 \longrightarrow 00:28:54.590$  But it's a good question.

NOTE Confidence: 0.827964603900909

00:28:54.590 --> 00:28:55.678 Probably something we should

NOTE Confidence: 0.827964603900909

 $00{:}28{:}55.678 \dashrightarrow 00{:}28{:}56.766$  devote more effort to.

NOTE Confidence: 0.831635475158691

00:28:57.380 --> 00:28:59.420 Yeah, well, I'm sure it'll

- NOTE Confidence: 0.831635475158691
- $00:28:59.420 \longrightarrow 00:29:00.646$  it'll definitely emerge.
- NOTE Confidence: 0.831635475158691
- 00:29:00.646 --> 00:29:03.908 Emerge as you get samples from your trial.
- NOTE Confidence: 0.831635475158691
- $00:29:03.910 \longrightarrow 00:29:05.586$  So it's really exciting.
- NOTE Confidence: 0.831635475158691
- 00:29:05.586 --> 00:29:08.799 And congratulations so I know we're at 12:31.
- NOTE Confidence: 0.831635475158691
- $00:29:08.800 \rightarrow 00:29:10.840$  Wherever so why don't we
- NOTE Confidence: 0.831635475158691
- $00:29:10.840 \longrightarrow 00:29:12.880$  will turn out to people?
- NOTE Confidence: 0.831635475158691
- 00:29:12.880 --> 00:29:15.328 Can submit questions to Barbara Online,
- NOTE Confidence: 0.831635475158691
- $00{:}29{:}15{.}330 \dashrightarrow 00{:}29{:}18{.}098$  but will turn now to our second speaker
- NOTE Confidence: 0.831635475158691
- $00:29:18.098 \rightarrow 00:29:20.716$  and very fortunate to have another
- NOTE Confidence: 0.831635475158691
- 00:29:20.716 --> 00:29:23.488 valued member of our faculty speaking.
- NOTE Confidence: 0.831635475158691
- 00:29:23.490 --> 00:29:25.956 Doctor Elizabeth Klaus is a professor
- NOTE Confidence: 0.831635475158691
- $00{:}29{:}25{.}956 \dashrightarrow 00{:}29{:}27{.}600$  of Biostatistics and neurosurgery.
- NOTE Confidence: 0.831635475158691
- $00{:}29{:}27.600 \dashrightarrow 00{:}29{:}30.222$  Focused not only on brain tumors
- NOTE Confidence: 0.831635475158691
- $00{:}29{:}30{.}222 \dashrightarrow 00{:}29{:}31{.}970$  but also the Epidemiology,
- NOTE Confidence: 0.831635475158691
- $00:29:31.970 \longrightarrow 00:29:33.718$  most notably the genetic
- NOTE Confidence: 0.831635475158691

 $00:29:33.718 \rightarrow 00:29:35.466$  Epidemiology of these malignancies.

NOTE Confidence: 0.831635475158691

 $00{:}29{:}35{.}470 \dashrightarrow 00{:}29{:}38{.}806$  She received her MD and PhD from Yale

NOTE Confidence: 0.831635475158691

 $00:29:38.806 \rightarrow 00:29:41.499$  and completed her surgery here in

NOTE Confidence: 0.831635475158691

 $00:29:41.499 \rightarrow 00:29:44.151$  their surgery and through her work

NOTE Confidence: 0.831635475158691

 $00:29:44.237 \longrightarrow 00:29:46.841$  she really has been an international

NOTE Confidence: 0.831635475158691

 $00{:}29{:}46.841 \dashrightarrow 00{:}29{:}49.454$  leader in in the investigation of

NOTE Confidence: 0.831635475158691

 $00:29:49.454 \rightarrow 00:29:51.639$  the Epidemiology of CNS Malignancy's,

NOTE Confidence: 0.831635475158691

 $00:29:51.640 \rightarrow 00:29:54.262$  most notably serving as the leader

NOTE Confidence: 0.831635475158691

 $00{:}29{:}54{.}262 \dashrightarrow 00{:}29{:}56{.}010$  of the Meningioma consortium,

NOTE Confidence: 0.831635475158691

00:29:56.010 --> 00:29:57.974 that meningioma Genome Wide

NOTE Confidence: 0.831635475158691

 $00{:}29{:}57{.}974 \dashrightarrow 00{:}29{:}58{.}956$  Association study.

NOTE Confidence: 0.831635475158691

00:29:58.960 --> 00:29:59.365 Also,

NOTE Confidence: 0.831635475158691

 $00:29:59.365 \rightarrow 00:30:02.605$  a leader of the AL Acoustic neuroma study,

NOTE Confidence: 0.831635475158691

 $00:30:02.610 \longrightarrow 00:30:05.730$  and we again were so pleased to have

NOTE Confidence: 0.831635475158691

 $00{:}30{:}05{.}730 \dashrightarrow 00{:}30{:}08{.}233$  talented people who bridge the gap

NOTE Confidence: 0.831635475158691

00:30:08.233 --> 00:30:10.705 of Epidemiology in biology of cancer

- NOTE Confidence: 0.831635475158691
- 00:30:10.785 --> 00:30:13.564 and Elizabeth thank you so much for
- NOTE Confidence: 0.831635475158691
- $00{:}30{:}13.564 \dashrightarrow 00{:}30{:}17.388$  sharing your work with us today.
- NOTE Confidence: 0.831635475158691
- $00{:}30{:}17{.}390 \dashrightarrow 00{:}30{:}18{.}326$  Thanks very much.
- NOTE Confidence: 0.831635475158691
- 00:30:18.326 --> 00:30:19.892 Can you see my slides?
- NOTE Confidence: 0.831635475158691
- 00:30:19.892 --> 00:30:20.204 OK,
- NOTE Confidence: 0.831635475158691
- $00{:}30{:}20{.}204 \dashrightarrow 00{:}30{:}20{.}828$  yes great.
- NOTE Confidence: 0.850167512893677
- $00:30:20.830 \longrightarrow 00:30:22.090$  So I'm going to
- NOTE Confidence: 0.850167512893677
- $00:30:22.090 \dashrightarrow 00:30:24.088$  talk a little bit about something
- NOTE Confidence: 0.850167512893677
- 00:30:24.088 --> 00:30:26.403 we've been working on an I do want
- NOTE Confidence: 0.850167512893677
- $00:30:26.403 \longrightarrow 00:30:28.571$  to note that this is work done in
- NOTE Confidence: 0.850167512893677
- $00:30:28.571 \rightarrow 00:30:30.386$  collaboration with Jeff Townsend's Group
- NOTE Confidence: 0.850167512893677
- $00{:}30{:}30{.}386 \dashrightarrow 00{:}30{:}33{.}040$  who I think you all know very well.
- NOTE Confidence: 0.850167512893677
- 00:30:33.040 --> 00:30:34.605 And Vincent Kenna Tarot as
- NOTE Confidence: 0.850167512893677
- $00{:}30{:}34{.}605 \dashrightarrow 00{:}30{:}35{.}857$  well as Steven Gaffney.
- NOTE Confidence: 0.850167512893677
- $00:30:35.860 \longrightarrow 00:30:37.425$  So despite all the things
- NOTE Confidence: 0.850167512893677

 $00:30:37.425 \longrightarrow 00:30:38.990$  that we've attempted to do,

NOTE Confidence: 0.850167512893677

 $00:30:38.990 \longrightarrow 00:30:40.868$  we still don't know much about

NOTE Confidence: 0.850167512893677

00:30:40.868 --> 00:30:42.120 risk factors for glioma.

NOTE Confidence: 0.850167512893677

 $00:30:42.120 \longrightarrow 00:30:43.940$  And we wanted to take a look

NOTE Confidence: 0.850167512893677

 $00:30:43.940 \dashrightarrow 00:30:45.939$  and see if they were different

NOTE Confidence: 0.850167512893677

 $00{:}30{:}45{.}939 \dashrightarrow 00{:}30{:}47{.}854$  methods that we could use.

NOTE Confidence: 0.850167512893677

 $00:30:47.860 \longrightarrow 00:30:50.184$  To see if we could tease out

NOTE Confidence: 0.850167512893677

 $00{:}30{:}50{.}184 \dashrightarrow 00{:}30{:}51{.}998$  both environmental and then also

NOTE Confidence: 0.850167512893677

00:30:51.998 --> 00:30:54.230 another hot topic is sex specific

NOTE Confidence: 0.850167512893677

 $00:30:54.230 \rightarrow 00:30:56.150$  signatures of glioma causation.

NOTE Confidence: 0.850167512893677

 $00{:}30{:}56{.}150 \dashrightarrow 00{:}30{:}59{.}548$  So you all know that gliomas are the most

NOTE Confidence: 0.850167512893677

 $00{:}30{:}59{.}548 \dashrightarrow 00{:}31{:}01{.}810$  common type of malignant brain tumor,

NOTE Confidence: 0.850167512893677

 $00:31:01.810 \rightarrow 00:31:04.826$  accounting for about 1/3 of all brain tumors,

NOTE Confidence: 0.850167512893677

 $00{:}31{:}04{.}830 \dashrightarrow 00{:}31{:}07{.}086$  and the majority of malignant tumors.

NOTE Confidence: 0.850167512893677

 $00:31:07.090 \rightarrow 00:31:09.226$  But they proved to be very

NOTE Confidence: 0.850167512893677

 $00{:}31{:}09{.}226 \dashrightarrow 00{:}31{:}11{.}899$  heterogeneous and we have not done a

00:31:11.899 --> 00:31:13.864 great job identifying risk factors,

NOTE Confidence: 0.850167512893677

 $00:31:13.870 \longrightarrow 00:31:17.055$  be they genetic or environmental for glioma.

NOTE Confidence: 0.850167512893677

 $00:31:17.060 \dashrightarrow 00:31:19.364$  And so we were interested in doing that,

NOTE Confidence: 0.850167512893677

 $00:31:19.370 \longrightarrow 00:31:21.694$  particularly in light of the poor outcomes

NOTE Confidence: 0.850167512893677

 $00:31:21.694 \rightarrow 00:31:24.476$  that we see with this group of patients.

NOTE Confidence: 0.850167512893677

 $00{:}31{:}24{.}480 \dashrightarrow 00{:}31{:}28{.}296$  So we do know that there are sex specific

NOTE Confidence: 0.850167512893677

 $00:31:28.296 \rightarrow 00:31:31.065$  differences in glioma risk and outcome and

NOTE Confidence: 0.850167512893677

 $00:31:31.065 \rightarrow 00:31:34.656$  the plots I have here are for all gliomas,

NOTE Confidence: 0.850167512893677

 $00{:}31{:}34{.}660 \dashrightarrow 00{:}31{:}36{.}284$  an then glioblastoma or

NOTE Confidence: 0.850167512893677

 $00:31:36.284 \rightarrow 00:31:38.314$  sort of an IDH positive.

NOTE Confidence: 0.850167512893677

00:31:38.320 --> 00:31:39.256 Excuse me,

NOTE Confidence: 0.850167512893677

 $00{:}31{:}39{.}256 \dashrightarrow 00{:}31{:}41{.}596$  IDH negative tumor and then

NOTE Confidence: 0.850167512893677

00:31:41.596 --> 00:31:43.000 lower grade gliomas.

NOTE Confidence: 0.850167512893677

00:31:43.000 --> 00:31:44.760 The males being the blue,

NOTE Confidence: 0.850167512893677

 $00{:}31{:}44.760 \dashrightarrow 00{:}31{:}47.040$  the females being the red.

 $00:31:47.040 \longrightarrow 00:31:49.068$  And it's interesting in that we

NOTE Confidence: 0.850167512893677

00:31:49.068 --> 00:31:50.904 see this sex specific difference

NOTE Confidence: 0.850167512893677

 $00:31:50.904 \rightarrow 00:31:52.979$  across the entire age range,

NOTE Confidence: 0.850167512893677

 $00{:}31{:}52{.}980 \dashrightarrow 00{:}31{:}55{.}206$  so it's a little bit different

NOTE Confidence: 0.850167512893677

 $00{:}31{:}55{.}206 \dashrightarrow 00{:}31{:}56{.}690$  than we see with,

NOTE Confidence: 0.850167512893677

 $00{:}31{:}56.690 \dashrightarrow 00{:}31{:}57.434$  for example,

NOTE Confidence: 0.850167512893677

 $00{:}31{:}57{.}434 \dashrightarrow 00{:}31{:}59{.}294$  meningiomas where we see the

NOTE Confidence: 0.850167512893677

00:31:59.294 --> 00:32:00.770 women having greater risk,

NOTE Confidence: 0.850167512893677

 $00{:}32{:}00{.}770 \dashrightarrow 00{:}32{:}02{.}858$  but the risk difference decreasing once

NOTE Confidence: 0.850167512893677

 $00:32:02.858 \rightarrow 00:32:04.850$  women passed through the menopause.

NOTE Confidence: 0.850167512893677

 $00{:}32{:}04.850 \dashrightarrow 00{:}32{:}07.028$  Whereas here we see the sex

NOTE Confidence: 0.850167512893677

 $00:32:07.028 \longrightarrow 00:32:08.920$  differences for glioma across the

NOTE Confidence: 0.850167512893677

 $00:32:08.920 \rightarrow 00:32:11.158$  age spectrum and across all subtypes,

NOTE Confidence: 0.850167512893677

 $00:32:11.160 \longrightarrow 00:32:13.260$  and so that obviously suggests

NOTE Confidence: 0.850167512893677

 $00{:}32{:}13.260 \dashrightarrow 00{:}32{:}15.360$  that other mechanisms in addition

NOTE Confidence: 0.850167512893677

 $00:32:15.432 \longrightarrow 00:32:17.469$  to a good sex hormones must be.

 $00{:}32{:}17{.}470 \dashrightarrow 00{:}32{:}19{.}222$  Are behind the difference men are

NOTE Confidence: 0.850167512893677

00:32:19.222 $\operatorname{-->}$ 00:32:21.187 at greater risk of being diagnosed

NOTE Confidence: 0.850167512893677

 $00{:}32{:}21.187 \dashrightarrow 00{:}32{:}22.297$  with the disease.

NOTE Confidence: 0.850167512893677

 $00:32:22.300 \longrightarrow 00:32:22.992$  And again,

NOTE Confidence: 0.850167512893677

 $00{:}32{:}22{.}992 \dashrightarrow 00{:}32{:}24{.}722$  that's across pretty much all

NOTE Confidence: 0.850167512893677

 $00{:}32{:}24.722 \dashrightarrow 00{:}32{:}26.861$  the subtypes and they also have

NOTE Confidence: 0.850167512893677

00:32:26.861 --> 00:32:28.591 lower survival in general then

NOTE Confidence: 0.850167512893677

 $00:32:28.591 \rightarrow 00:32:30.560$  for females across all subtypes.

NOTE Confidence: 0.850167512893677

 $00{:}32{:}30{.}560 \dashrightarrow 00{:}32{:}32{.}919$  So we've looked at this a little

NOTE Confidence: 0.850167512893677

00:32:32.919 --> 00:32:35.351 bit and I've been lucky enough

NOTE Confidence: 0.850167512893677

00:32:35.351 --> 00:32:38.045 to collaborate with a group of

NOTE Confidence: 0.850167512893677

 $00{:}32{:}38.045 \dashrightarrow 00{:}32{:}39.919$  individuals called the glioma.

NOTE Confidence: 0.850167512893677

 $00{:}32{:}39{.}920 \dashrightarrow 00{:}32{:}41{.}548$  International Case Controls Consortium,

NOTE Confidence: 0.850167512893677

 $00{:}32{:}41{.}548 \dashrightarrow 00{:}32{:}43{.}990$  and that's led by Melissa Bondy,

NOTE Confidence: 0.850167512893677

 $00{:}32{:}43.990 \dashrightarrow 00{:}32{:}46.839$  initially at MD Anderson, then it Baylor.

 $00:32:46.840 \longrightarrow 00:32:49.276$  Now she heads up the Epidemiology

NOTE Confidence: 0.850167512893677

 $00{:}32{:}49{.}276 \dashrightarrow 00{:}32{:}50{.}494$  section at Stanford,

NOTE Confidence: 0.850167512893677

 $00:32:50.500 \dashrightarrow 00:32:53.027$  but we were able to gather over

NOTE Confidence: 0.850167512893677

 $00:32:53.027 \rightarrow 00:32:55.390 10,000$  cases and 10,000 controls,

NOTE Confidence: 0.850167512893677

 $00{:}32{:}55{.}390 \dashrightarrow 00{:}32{:}58{.}102$  and so these are essentially looking

NOTE Confidence: 0.850167512893677

 $00{:}32{:}58{.}102 \dashrightarrow 00{:}32{:}59{.}910$  at constitutional or germline

NOTE Confidence: 0.850167512893677

 $00:32:59.980 \longrightarrow 00:33:01.348$  risk alleles by sex.

NOTE Confidence: 0.850167512893677

 $00{:}33{:}01{.}350 \dashrightarrow 00{:}33{:}03{.}660$  So if I can draw your attention

NOTE Confidence: 0.850167512893677

 $00:33:03.660 \longrightarrow 00:33:05.479$  to the table over here,

NOTE Confidence: 0.850167512893677

 $00{:}33{:}05{.}480 \dashrightarrow 00{:}33{:}07{.}316$  these are the variants that we

NOTE Confidence: 0.850167512893677

 $00{:}33{:}07{.}316 \dashrightarrow 00{:}33{:}09{.}019$  found to be significantly different

NOTE Confidence: 0.850167512893677

00:33:09.019 --> 00:33:10.288 males versus females.

NOTE Confidence: 0.850167512893677

00:33:10.290 - 00:33:11.666 Males being the blue,

NOTE Confidence: 0.850167512893677

 $00:33:11.666 \longrightarrow 00:33:13.386$  an females being the red.

NOTE Confidence: 0.850167512893677

 $00:33:13.390 \longrightarrow 00:33:15.454$  So we did certainly find differences

NOTE Confidence: 0.850167512893677

 $00:33:15.454 \rightarrow 00:33:16.830$  at the germline level,

- NOTE Confidence: 0.850167512893677
- $00{:}33{:}16.830 \dashrightarrow 00{:}33{:}18.762$  but we were also interested in
- NOTE Confidence: 0.850167512893677
- $00:33:18.762 \longrightarrow 00:33:20.853$  looking at things at the tumor
- NOTE Confidence: 0.850167512893677
- $00:33:20.853 \longrightarrow 00:33:22.325$  or their cinematic level.
- NOTE Confidence: 0.850167512893677
- $00:33:22.330 \dashrightarrow 00:33:25.090$ 0 Sex is a biologic variables I mentioned.
- NOTE Confidence: 0.850167512893677
- $00:33:25.090 \longrightarrow 00:33:27.148$  This is a very hot topic.
- NOTE Confidence: 0.841646373271942
- $00:33:27.150 \rightarrow 00:33:29.607$  Now we obviously know there are biologic
- NOTE Confidence: 0.841646373271942
- $00:33:29.607 \dashrightarrow 00:33:31.359$  differences between males and females.
- NOTE Confidence: 0.841646373271942
- $00:33:31.360 \longrightarrow 00:33:33.328$  There's also some thought as to
- NOTE Confidence: 0.841646373271942
- $00{:}33{:}33{.}328 \dashrightarrow 00{:}33{:}34{.}640$  whether there's variation in
- NOTE Confidence: 0.841646373271942
- 00:33:34.695 --> 00:33:36.390 the prevalence of risk factors,
- NOTE Confidence: 0.841646373271942
- $00:33:36.390 \longrightarrow 00:33:37.865$  and then also whether there's
- NOTE Confidence: 0.841646373271942
- $00{:}33{:}37{.}865 \dashrightarrow 00{:}33{:}40{.}204$  a difference in sort of a gene
- NOTE Confidence: 0.841646373271942
- $00{:}33{:}40{.}204 \dashrightarrow 00{:}33{:}41{.}407$  by environmental interaction.
- NOTE Confidence: 0.841646373271942
- 00:33:41.410 --> 00:33:42.415 So, for example,
- NOTE Confidence: 0.841646373271942
- $00:33:42.415 \dashrightarrow 00:33:44.425$  and this has long been postulated,
- NOTE Confidence: 0.841646373271942

 $00:33:44.430 \longrightarrow 00:33:46.470$  but it's really been pretty difficult

NOTE Confidence: 0.841646373271942

 $00{:}33{:}46{.}470 \dashrightarrow 00{:}33{:}48{.}807$  to prove that males in particular are

NOTE Confidence: 0.841646373271942

 $00:33:48.807 \rightarrow 00:33:51.353$  more likely to be exposed to work like

NOTE Confidence: 0.841646373271942

 $00:33:51.353 \rightarrow 00:33:53.810$  toxins that might be associated with risk,

NOTE Confidence: 0.841646373271942

 $00{:}33{:}53{.}810 \dashrightarrow 00{:}33{:}56{.}546$  and so that was one of the things

NOTE Confidence: 0.841646373271942

 $00{:}33{:}56{.}546 \dashrightarrow 00{:}33{:}58{.}826$  we wanted to look at as well.

NOTE Confidence: 0.841646373271942

 $00:33:58.830 \rightarrow 00:34:01.510$  And in part, why we divided our analysis.

NOTE Confidence: 0.841646373271942

 $00:34:01.510 \longrightarrow 00:34:03.390$  By sex.

NOTE Confidence: 0.841646373271942

 $00:34:03.390 \longrightarrow 00:34:05.484$  So there's two goals and what

NOTE Confidence: 0.841646373271942

 $00:34:05.484 \longrightarrow 00:34:07.850$  I'm going to talk about today.

NOTE Confidence: 0.841646373271942

 $00{:}34{:}07{.}850 \dashrightarrow 00{:}34{:}10{.}454$  We wanted to look at the relative

NOTE Confidence: 0.841646373271942

 $00{:}34{:}10{.}454 \dashrightarrow 00{:}34{:}12{.}451$  contribution and this is based on

NOTE Confidence: 0.841646373271942

 $00{:}34{:}12{.}451 \dashrightarrow 00{:}34{:}14{.}935$  some of the work that I know you've

NOTE Confidence: 0.841646373271942

 $00{:}34{:}14{.}935 \dashrightarrow 00{:}34{:}17{.}530$  already appreciated with Jeff Townsend,

NOTE Confidence: 0.841646373271942

 $00:34:17.530 \rightarrow 00:34:19.385$  but we're applying it specifically

NOTE Confidence: 0.841646373271942

00:34:19.385 --> 00:34:20.498 now to glioma,

- NOTE Confidence: 0.841646373271942
- $00:34:20.500 \longrightarrow 00:34:22.360$  but looking at the relative
- NOTE Confidence: 0.841646373271942
- $00{:}34{:}22{.}360 \dashrightarrow 00{:}34{:}24{.}220$  contribution of cancer cell lineages,
- NOTE Confidence: 0.841646373271942
- $00{:}34{:}24{.}220 \dashrightarrow 00{:}34{:}25{.}708$  proliferation and survival of
- NOTE Confidence: 0.841646373271942
- $00:34:25.708 \longrightarrow 00:34:26.824$  single nucleotide mutations,
- NOTE Confidence: 0.841646373271942
- $00:34:26.830 \dashrightarrow 00:34:29.062$  and we divided our study subjects
- NOTE Confidence: 0.841646373271942
- $00{:}34{:}29.062 \dashrightarrow 00{:}34{:}30.550$  up by IDH mutation.
- NOTE Confidence: 0.841646373271942
- 00:34:30.550 --> 00:34:32.776 And, as most of you know,
- NOTE Confidence: 0.841646373271942
- $00{:}34{:}32{.}780 \dashrightarrow 00{:}34{:}35{.}012$  IDH mutation is one of the
- NOTE Confidence: 0.841646373271942
- $00{:}34{:}35{.}012 \dashrightarrow 00{:}34{:}36{.}500$  key dividers into the.
- NOTE Confidence: 0.841646373271942
- $00:34:36.500 \rightarrow 00:34:38.915$  The higher in the lower grade tumors,
- NOTE Confidence: 0.841646373271942
- $00:34:38.920 \rightarrow 00:34:40.640$  and certainly a prognostic factor,
- NOTE Confidence: 0.841646373271942
- $00:34:40.640 \longrightarrow 00:34:43.745$  as well as a factor in response to treatment.
- NOTE Confidence: 0.841646373271942
- $00:34:43.750 \longrightarrow 00:34:45.470$  We also wanted to quantify,
- NOTE Confidence: 0.841646373271942
- $00{:}34{:}45{.}470 \dashrightarrow 00{:}34{:}47{.}535$  and this is something that is a
- NOTE Confidence: 0.841646373271942
- 00:34:47.535 --> 00:34:49.199 little bit new to Epidemiology
- NOTE Confidence: 0.841646373271942

 $00:34:49.199 \longrightarrow 00:34:51.670$  in terms of how we've tried to

NOTE Confidence: 0.841646373271942

 $00{:}34{:}51{.}670 \dashrightarrow 00{:}34{:}53{.}059$  identify risk exposures.

NOTE Confidence: 0.841646373271942

00:34:53.060 - 00:34:54.975 Typically we've done things like

NOTE Confidence: 0.841646373271942

00:34:54.975 - 00:34:56.890 large case control studies where

NOTE Confidence: 0.841646373271942

00:34:56.950 --> 00:34:58.931 we look at large numbers of people

NOTE Confidence: 0.841646373271942

 $00:34:58.931 \longrightarrow 00:35:00.310$  that have the disease,

NOTE Confidence: 0.841646373271942

00:35:00.310 -> 00:35:02.035 compare them to large numbers

NOTE Confidence: 0.841646373271942

 $00:35:02.035 \longrightarrow 00:35:03.760$  of people without the disease,

NOTE Confidence: 0.841646373271942

 $00{:}35{:}03{.}760 \dashrightarrow 00{:}35{:}05{.}842$  and look at things like question naire

NOTE Confidence: 0.841646373271942

 $00:35:05.842 \rightarrow 00:35:06.883$  or work pic.

NOTE Confidence: 0.841646373271942

 $00:35:06.890 \dashrightarrow 00:35:09.626$  Exposure and see if we can figure out

NOTE Confidence: 0.841646373271942

 $00:35:09.626 \dashrightarrow 00:35:11.757$  differences between the cases and controls.

NOTE Confidence: 0.841646373271942

 $00:35:11.760 \longrightarrow 00:35:13.500$  So what we're doing now,

NOTE Confidence: 0.841646373271942

 $00:35:13.500 \rightarrow 00:35:15.565$  and this is sort of an emerging

NOTE Confidence: 0.841646373271942

00:35:15.565 --> 00:35:17.330 field in cancer Epidemiology,

NOTE Confidence: 0.841646373271942

 $00:35:17.330 \longrightarrow 00:35:19.787$  is to look at the cosmic cancer

 $00{:}35{:}19.787 \dashrightarrow 00{:}35{:}21.511$  mutational signatures in tumors and

NOTE Confidence: 0.841646373271942

 $00{:}35{:}21{.}511 \dashrightarrow 00{:}35{:}23{.}618$  see if we can then backtrack match

NOTE Confidence: 0.841646373271942

 $00:35:23.618 \rightarrow 00:35:25.677$  it to possible risk exposures,

NOTE Confidence: 0.841646373271942

 $00:35:25.680 \rightarrow 00:35:27.787$  and one of the things we're hoping

NOTE Confidence: 0.841646373271942

00:35:27.787 --> 00:35:30.870 to do in the future is to go back to

NOTE Confidence: 0.841646373271942

 $00{:}35{:}30{.}870 \dashrightarrow 00{:}35{:}33{.}127$  our cohorts and studies for which

NOTE Confidence: 0.841646373271942

 $00{:}35{:}33{.}127 \dashrightarrow 00{:}35{.}35{.}262$  we collected good occupational data

NOTE Confidence: 0.841646373271942

 $00:35:35.262 \rightarrow 00:35:38.556$  and see if we can match it up to.

NOTE Confidence: 0.841646373271942

 $00{:}35{:}38{.}560 \dashrightarrow 00{:}35{:}42{.}131$  Mutational signatures So the methods

NOTE Confidence: 0.841646373271942

 $00:35:42.131 \longrightarrow 00:35:44.153$  I'll talk a little bit about.

NOTE Confidence: 0.841646373271942

 $00:35:44.160 \longrightarrow 00:35:45.516$  I am highlighting here.

NOTE Confidence: 0.841646373271942

 $00{:}35{:}45{.}516 \dashrightarrow 00{:}35{:}47{.}940$  Jeff's paper that he had in J&CI

NOTE Confidence: 0.841646373271942

00:35:47.940 --> 00:35:48.888 two years ago,

NOTE Confidence: 0.841646373271942

 $00{:}35{:}48.890 \dashrightarrow 00{:}35{:}50.962$  and I think you've seen some of

NOTE Confidence: 0.841646373271942

 $00:35:50.962 \dashrightarrow 00:35:52.949$  these sorts of methods applied,

 $00:35:52.950 \longrightarrow 00:35:55.000$  in particular to actually head

NOTE Confidence: 0.841646373271942

 $00{:}35{:}55{.}000 \dashrightarrow 00{:}35{:}56{.}230$  and neck cancer.

NOTE Confidence: 0.841646373271942

 $00:35:56.230 \longrightarrow 00:35:58.670$  So the Cancer Genome Atlas,

NOTE Confidence: 0.841646373271942

00:35:58.670 - 00:36:01.100 and others, including the glioma

NOTE Confidence: 0.841646373271942

00:36:01.100 --> 00:36:02.558 Longitudinal Analysis Consortium,

NOTE Confidence: 0.841646373271942

 $00{:}36{:}02{.}560 \dashrightarrow 00{:}36{:}05{.}969$  or Glass, which is led by roll.

NOTE Confidence: 0.841646373271942

 $00:36:05.970 \longrightarrow 00:36:06.968$  Their Hokage,

NOTE Confidence: 0.841646373271942

 $00{:}36{:}06{.}968 \dashrightarrow 00{:}36{:}11{.}330$  Jackson Labs and which I'm also a member of.

NOTE Confidence: 0.841646373271942

 $00:36:11.330 \longrightarrow 00:36:13.810$  So these groups have identified

NOTE Confidence: 0.841646373271942

 $00{:}36{:}13.810 \dashrightarrow 00{:}36{:}16.838$  the most common genetic changes in

NOTE Confidence: 0.841646373271942

00:36:16.838 --> 00:36:19.604 primary glioma tumors including TP 53,

NOTE Confidence: 0.841646373271942

00:36:19.610 --> 00:36:20.080 IDH,

NOTE Confidence: 0.841646373271942

 $00{:}36{:}20.080 \dashrightarrow 00{:}36{:}22.430$  EGFR with the relative importance

NOTE Confidence: 0.841646373271942

 $00:36:22.430 \longrightarrow 00:36:25.403$  of these mutations and how they

NOTE Confidence: 0.841646373271942

 $00:36:25.403 \longrightarrow 00:36:26.927$  relate to tumorigenesis.

NOTE Confidence: 0.841646373271942

 $00:36:26.930 \longrightarrow 00:36:28.366$  Is not well known,

 $00:36:28.366 \longrightarrow 00:36:31.053$  so one of the things that we've

NOTE Confidence: 0.841646373271942

 $00:36:31.053 \rightarrow 00:36:32.400$  been working on,

NOTE Confidence: 0.841646373271942

 $00:36:32.400 \longrightarrow 00:36:34.878$  and Jeff has been a leader in

NOTE Confidence: 0.841646373271942

 $00:36:34.878 \longrightarrow 00:36:35.940$  is defining this

NOTE Confidence: 0.841837286949158

00:36:36.025 --> 00:36:37.489 cancer affect size.

NOTE Confidence: 0.841837286949158

 $00:36:37.490 \longrightarrow 00:36:39.686$  So this metric of the relative

NOTE Confidence: 0.841837286949158

 $00{:}36{:}39{.}686$  -->  $00{:}36{:}41{.}641$  overa<br/>bundance of variance due to

NOTE Confidence: 0.841837286949158

00:36:41.641 -> 00:36:43.349 their contributions to survival,

NOTE Confidence: 0.841837286949158

 $00:36:43.350 \longrightarrow 00:36:44.914$  indivision versus what you're

NOTE Confidence: 0.841837286949158

 $00:36:44.914 \rightarrow 00:36:46.869$  actually seeing in the tumor.

NOTE Confidence: 0.841837286949158

 $00{:}36{:}46.870 \dashrightarrow 00{:}36{:}49.607$  So we're quantifying the cancer affect size.

NOTE Confidence: 0.841837286949158

 $00{:}36{:}49{.}610 \dashrightarrow 00{:}36{:}51{.}560$  We're using single nucleotide mutations,

NOTE Confidence: 0.841837286949158

 $00{:}36{:}51{.}560 \dashrightarrow 00{:}36{:}54{.}535$  and then we basically do a scaled

NOTE Confidence: 0.841837286949158

 $00{:}36{:}54{.}535 \dashrightarrow 00{:}36{:}56{.}974$  selection coefficient for the for the

NOTE Confidence: 0.841837286949158

 $00{:}36{:}56{.}974 \dashrightarrow 00{:}36{:}59{.}140$  different variants we look at it.

 $00:36:59.140 \longrightarrow 00:37:01.288$  By sex and by IDH subtype.

NOTE Confidence: 0.841837286949158

 $00{:}37{:}01.290 \dashrightarrow 00{:}37{:}04.107$  And so we're trying to get a feel for

NOTE Confidence: 0.841837286949158

 $00{:}37{:}04{.}107 \dashrightarrow 00{:}37{:}06{.}482$  whether this would help us explain

NOTE Confidence: 0.841837286949158

 $00:37:06.482 \longrightarrow 00:37:08.467$  any differences in the glioma,

NOTE Confidence: 0.841837286949158

 $00:37:08.470 \longrightarrow 00:37:11.350$  risk and outcome that we see by sex.

NOTE Confidence: 0.841837286949158

 $00:37:11.350 \longrightarrow 00:37:13.854$  And then we're going to move on to NOTE Confidence: 0.841837286949158

 $00{:}37{:}13.854 \dashrightarrow 00{:}37{:}16.542$  the cosmic mutations so I won't go

NOTE Confidence: 0.841837286949158

 $00:37:16.542 \longrightarrow 00:37:18.527$  into the gory statistical detail.

NOTE Confidence: 0.841837286949158

 $00{:}37{:}18.530 \dashrightarrow 00{:}37{:}20.678$  This is drawn from Jeffs paper,

NOTE Confidence: 0.841837286949158

 $00:37:20.680 \rightarrow 00:37:22.056$  but basically you're comparing

NOTE Confidence: 0.841837286949158

 $00{:}37{:}22.056 \dashrightarrow 00{:}37{:}23.776$  expected to observed so expected

NOTE Confidence: 0.841837286949158

00:37:23.776 --> 00:37:25.349 number of synonymous mutations,

NOTE Confidence: 0.841837286949158

 $00:37:25.350 \longrightarrow 00:37:27.282$  and then we're looking at the

NOTE Confidence: 0.841837286949158

 $00{:}37{:}27.282 \dashrightarrow 00{:}37{:}29.330$  rate at which the mutations.

NOTE Confidence: 0.841837286949158

00:37:29.330 --> 00:37:30.282 Actually occur.

NOTE Confidence: 0.841837286949158

 $00:37:30.282 \rightarrow 00:37:33.138$  The data that we're using here,

 $00:37:33.140 \longrightarrow 00:37:35.804$  our whole exome sequencing data from a pretty

NOTE Confidence: 0.841837286949158

00:37:35.804 --> 00:37:38.225 good size data set in terms of glioma,

NOTE Confidence: 0.841837286949158

 $00{:}37{:}38{.}230 \dashrightarrow 00{:}37{:}40{.}132$  so about 1100 and these are

NOTE Confidence: 0.841837286949158

 $00:37:40.132 \rightarrow 00:37:41.083$  all adult patients.

NOTE Confidence: 0.841837286949158

 $00{:}37{:}41.090 \dashrightarrow 00{:}37{:}42.290$  There's no pediatric patients

NOTE Confidence: 0.841837286949158

 $00:37:42.290 \longrightarrow 00:37:44.830$  in here and we drew it from the

NOTE Confidence: 0.841837286949158

00:37:44.830 --> 00:37:46.178 Cancer Genome Atlas study.

NOTE Confidence: 0.841837286949158

 $00{:}37{:}46.180 \dashrightarrow 00{:}37{:}47.356$  And as I mentioned,

NOTE Confidence: 0.841837286949158

00:37:47.356 --> 00:37:50.246 I know some of you may be aware of

NOTE Confidence: 0.841837286949158

 $00:37:50.246 \longrightarrow 00:37:52.110$  what glasses, so it's an effort.

NOTE Confidence: 0.841837286949158

00:37:52.110 --> 00:37:54.440 As I mentioned led by role Verhaag,

NOTE Confidence: 0.841837286949158

 $00:37:54.440 \longrightarrow 00:37:56.760$  but which yell is also a member of

NOTE Confidence: 0.841837286949158

 $00:37:56.760 \rightarrow 00:37:59.210$  looking at not only the initial tumors,

NOTE Confidence: 0.841837286949158

 $00{:}37{:}59{.}210 \dashrightarrow 00{:}38{:}00{.}510$  but the humours overtime.

NOTE Confidence: 0.841837286949158

 $00:38:00.510 \longrightarrow 00:38:02.135$  So how do they change?

00:38:02.140 --> 00:38:04.018 In terms of their genetic makeup,

NOTE Confidence: 0.841837286949158

 $00{:}38{:}04{.}020 \dashrightarrow 00{:}38{:}06{.}516$  when we do nothing to them when we

NOTE Confidence: 0.841837286949158

00:38:06.516 --> 00:38:08.399 do chemotherapy or we do radiation,

NOTE Confidence: 0.841837286949158

 $00:38:08.400 \dashrightarrow 00:38:11.176$  or a combination of all the above and

NOTE Confidence: 0.841837286949158

00:38:11.176 --> 00:38:13.615 what changes do we see and what do

NOTE Confidence: 0.841837286949158

00:38:13.615 --> 00:38:15.995 we learn from that in terms of what NOTE Confidence: 0.841837286949158

 $00:38:15.995 \rightarrow 00:38:18.103$  we should or should not be doing?

NOTE Confidence: 0.841837286949158

 $00:38:18.103 \rightarrow 00:38:20.920$  And then we also used a lot of data.

NOTE Confidence: 0.841837286949158

 $00{:}38{:}20{.}920 \dashrightarrow 00{:}38{:}22{.}798$  All of this is readily available

NOTE Confidence: 0.841837286949158

 $00:38:22.798 \longrightarrow 00:38:23.737$  off the Internet,

NOTE Confidence: 0.841837286949158

 $00{:}38{:}23.740 \dashrightarrow 00{:}38{:}25.618$  but we use tissue specific mutational

NOTE Confidence: 0.841837286949158

 $00{:}38{:}25.618 \dashrightarrow 00{:}38{:}26.870$  covariance and this helped.

NOTE Confidence: 0.841837286949158

 $00:38:26.870 \longrightarrow 00:38:29.040$  Just figure out what sort of mutation

NOTE Confidence: 0.841837286949158

 $00{:}38{:}29{.}040 \dashrightarrow 00{:}38{:}30{.}619$  rate calculations we should use.

NOTE Confidence: 0.841837286949158

 $00{:}38{:}30{.}620 \dashrightarrow 00{:}38{:}32{.}881$  Gave us a little bit of information

NOTE Confidence: 0.841837286949158

 $00:38:32.881 \dashrightarrow 00:38:33.850$  about replication timing.

 $00:38:33.850 \dashrightarrow 00:38:35.794$  And some of the other datasets

NOTE Confidence: 0.841837286949158

 $00:38:35.794 \rightarrow 00:38:37.090$  that are listed here.

NOTE Confidence: 0.841837286949158

 $00:38:37.090 \longrightarrow 00:38:39.166$  So here's some of the results.

NOTE Confidence: 0.841837286949158

 $00:38:39.170 \longrightarrow 00:38:42.275$  Just to take you through it a little bit.

NOTE Confidence: 0.841837286949158

 $00:38:42.280 \longrightarrow 00:38:44.776$  So I have a divided by tumor type

NOTE Confidence: 0.841837286949158

 $00:38:44.776 \longrightarrow 00:38:47.118$  and it's by seksan by mutation.

NOTE Confidence: 0.841837286949158

 $00{:}38{:}47{.}120 \dashrightarrow 00{:}38{:}49{.}402$  So the wild type tumors who would

NOTE Confidence: 0.841837286949158

 $00:38:49.402 \dashrightarrow 00:38:51.620$  be considered the higher grade are

NOTE Confidence: 0.841837286949158

 $00{:}38{:}51{.}620 \dashrightarrow 00{:}38{:}53{.}570$  primarily the glioblastoma tumors are

NOTE Confidence: 0.841837286949158

 $00:38:53.570 \dashrightarrow 00:38:56.465$  in the first 2 rows and the IDH mutant,

NOTE Confidence: 0.841837286949158

 $00:38:56.470 \longrightarrow 00:38:57.850$  which would more typically

NOTE Confidence: 0.841837286949158

 $00{:}38{:}57{.}850 \dashrightarrow 00{:}38{:}59{.}575$  be the lower grade tumors.

NOTE Confidence: 0.841837286949158

 $00{:}38{:}59{.}580 \dashrightarrow 00{:}39{:}01{.}995$  And then I have males versus females,

NOTE Confidence: 0.841837286949158

 $00{:}39{:}02.000 \dashrightarrow 00{:}39{:}03.017$  males versus females,

NOTE Confidence: 0.841837286949158

 $00{:}39{:}03{.}017 \dashrightarrow 00{:}39{:}05{.}051$  and then there's sort of a

00:39:05.051 --> 00:39:06.499 cancer affect size here.

NOTE Confidence: 0.841837286949158

 $00{:}39{:}06{.}500 \dashrightarrow 00{:}39{:}08{.}588$  The blue is non coding region.

NOTE Confidence: 0.841837286949158

 $00:39:08.590 \longrightarrow 00:39:10.445$  And the red is coding so you

NOTE Confidence: 0.841837286949158

 $00:39:10.445 \longrightarrow 00:39:12.446$  can see the patterns are quite

NOTE Confidence: 0.841837286949158

 $00{:}39{:}12{.}446 \dashrightarrow 00{:}39{:}14{.}714$  different for what might be called

NOTE Confidence: 0.841837286949158

 $00:39:14.714 \longrightarrow 00:39:16.688$  the low and the high grade,

NOTE Confidence: 0.841837286949158

 $00{:}39{:}16.690 \dashrightarrow 00{:}39{:}19.060$  the IDH mutant tumors had few

NOTE Confidence: 0.841837286949158

 $00:39:19.060 \rightarrow 00:39:20.245$  unique recurrent substitutions.

NOTE Confidence: 0.841837286949158

 $00{:}39{:}20{.}250 \dashrightarrow 00{:}39{:}22{.}567$  All of them were in coding regions,

NOTE Confidence: 0.841837286949158

 $00:39:22.570 \rightarrow 00:39:24.220$  whereas the wild type tumors,

NOTE Confidence: 0.841837286949158

 $00:39:24.220 \longrightarrow 00:39:26.201$  and obviously this is in part what

NOTE Confidence: 0.841837286949158

 $00{:}39{:}26{.}201 \dashrightarrow 00{:}39{:}28{.}643$  makes them so hard to manage is

NOTE Confidence: 0.841837286949158

 $00:39:28.643 \rightarrow 00:39:30.175$  they exhibited many substitutions,

NOTE Confidence: 0.850281715393066

 $00:39:30.180 \longrightarrow 00:39:32.028$  but they were primarily

NOTE Confidence: 0.850281715393066

 $00:39:32.028 \longrightarrow 00:39:33.876$  in non coding regions.

NOTE Confidence: 0.850281715393066

 $00:39:33.880 \longrightarrow 00:39:35.444$  So here's another picture.

00:39:35.444 --> 00:39:38.270 A little busy but divided once again,

NOTE Confidence: 0.850281715393066

 $00{:}39{:}38{.}270 \dashrightarrow 00{:}39{:}40{.}986$  the IDH mutant or the lower grade

NOTE Confidence: 0.850281715393066

 $00:39:40.986 \longrightarrow 00:39:42.660$  tumors are presented first.

NOTE Confidence: 0.850281715393066

 $00:39:42.660 \rightarrow 00:39:44.650$  The wild types are second,

NOTE Confidence: 0.850281715393066

00:39:44.650 - 00:39:47.107 and there's female male, female, male,

NOTE Confidence: 0.850281715393066

 $00:39:47.107 \rightarrow 00:39:51.220$  and So what we're looking at here is that.

NOTE Confidence: 0.850281715393066

 $00:39:51.220 \longrightarrow 00:39:53.105$  Items that top the list

NOTE Confidence: 0.850281715393066

 $00:39:53.105 \longrightarrow 00:39:54.613$  are the most important.

NOTE Confidence: 0.850281715393066

 $00:39:54.620 \dashrightarrow 00:39:57.428$  The size of the circle that is attached

NOTE Confidence: 0.850281715393066

 $00:39:57.428 \longrightarrow 00:39:59.401$  to them measures the prevalence

NOTE Confidence: 0.850281715393066

 $00:39:59.401 \longrightarrow 00:40:02.173$  so there can be kind of this.

NOTE Confidence: 0.850281715393066

 $00:40:02.180 \longrightarrow 00:40:04.622$  Disconnect as to what is important

NOTE Confidence: 0.850281715393066

 $00{:}40{:}04{.}622 \dashrightarrow 00{:}40{:}06{.}947$  and how frequently it occurs so

NOTE Confidence: 0.850281715393066

 $00{:}40{:}06{.}947 \dashrightarrow 00{:}40{:}09{.}443$  we can see that in the low grades

NOTE Confidence: 0.850281715393066

 $00{:}40{:}09{.}522 \dashrightarrow 00{:}40{:}11.627$  it's pretty much as expected.

 $00:40:11.630 \longrightarrow 00:40:12.764$  Previously reported mutations

NOTE Confidence: 0.850281715393066

 $00:40:12.764 \longrightarrow 00:40:15.410$  in IDH one and two TP 53.

NOTE Confidence: 0.850281715393066

 $00:40:15.410 \rightarrow 00:40:18.056$  Some of the other classics were confirmed,

NOTE Confidence: 0.850281715393066

 $00:40:18.060 \longrightarrow 00:40:19.584$  but what's interesting is

NOTE Confidence: 0.850281715393066

 $00:40:19.584 \longrightarrow 00:40:22.290$  if we go here to the IDH.

NOTE Confidence: 0.850281715393066

 $00{:}40{:}22.290 \dashrightarrow 00{:}40{:}24.612$  Wild type tumors the most important

NOTE Confidence: 0.850281715393066

 $00{:}40{:}24.612 \dashrightarrow 00{:}40{:}26.622$  with respect to cancer affect

NOTE Confidence: 0.850281715393066

 $00:40:26.622 \rightarrow 00:40:28.968$  gene is this low prevalence right?

NOTE Confidence: 0.850281715393066

 $00{:}40{:}28{.}970 \dashrightarrow 00{:}40{:}31{.}358$  You can see that the circle

NOTE Confidence: 0.850281715393066

 $00:40:31.358 \rightarrow 00:40:34.079$  that matches up to it is small,

NOTE Confidence: 0.850281715393066

 $00:40:34.080 \rightarrow 00:40:36.824$  not large like we see for IDH.

NOTE Confidence: 0.850281715393066

 $00:40:36.830 \longrightarrow 00:40:39.602$  Is this B RAF V 600 E so we

NOTE Confidence: 0.850281715393066

 $00:40:39.602 \longrightarrow 00:40:41.938$  know that it's important.

NOTE Confidence: 0.850281715393066

 $00{:}40{:}41{.}940 \dashrightarrow 00{:}40{:}44{.}022$  It turns out that it looks

NOTE Confidence: 0.850281715393066

 $00:40:44.022 \rightarrow 00:40:46.260$  like it's the most important,

NOTE Confidence: 0.850281715393066

 $00:40:46.260 \longrightarrow 00:40:48.225$  but obviously it doesn't occur

 $00:40:48.225 \rightarrow 00:40:49.797$  that frequently but interesting.

NOTE Confidence: 0.850281715393066

 $00:40:49.800 \rightarrow 00:40:52.600$  What drives some of these gliomas here?

NOTE Confidence: 0.850281715393066

 $00{:}40{:}52.600 \dashrightarrow 00{:}40{:}54.584$  The other thing we looked at is do

NOTE Confidence: 0.850281715393066

 $00{:}40{:}54{.}584 \dashrightarrow 00{:}40{:}57{.}175$  males and females show the same pattern

NOTE Confidence: 0.850281715393066

 $00:40:57.175 \rightarrow 00:40:58.803$  of what significantly overburdened,

NOTE Confidence: 0.850281715393066

 $00{:}40{:}58{.}810 \dashrightarrow 00{:}41{:}01{.}512$  and there were a lot of similarities

NOTE Confidence: 0.850281715393066

 $00:41:01.512 \longrightarrow 00:41:04.144$  the way that we have this broken

NOTE Confidence: 0.850281715393066

 $00:41:04.144 \rightarrow 00:41:06.860$  up here is each panel is a gene.

NOTE Confidence: 0.850281715393066

 $00:41:06.860 \longrightarrow 00:41:09.308$  The mutants come first in each

NOTE Confidence: 0.850281715393066

 $00:41:09.308 \longrightarrow 00:41:11.822$  panel and then within each panel

NOTE Confidence: 0.850281715393066

 $00:41:11.822 \rightarrow 00:41:14.629$  we've got the females in the mails.

NOTE Confidence: 0.850281715393066

 $00:41:14.630 \longrightarrow 00:41:16.854$  So we did see some differences,

NOTE Confidence: 0.850281715393066

00:41:16.854 $\operatorname{-->}$ 00:41:19.026 although overall most the things the

NOTE Confidence: 0.850281715393066

 $00{:}41{:}19{.}026 \dashrightarrow 00{:}41{:}21{.}397$  males and females showed were similar,

NOTE Confidence: 0.850281715393066

 $00{:}41{:}21{.}400 \dashrightarrow 00{:}41{:}24{.}400$  but we did see differences in the P3K

00:41:24.400 --> 00:41:27.405 pathway, so an IDH mutant, tumors the PK.

NOTE Confidence: 0.850281715393066

00:41:27.410 --> 00:41:29.552 Three CA mutations were located in

NOTE Confidence: 0.850281715393066

 $00:41:29.552 \longrightarrow 00:41:31.550$  the helical domain for females,

NOTE Confidence: 0.850281715393066

 $00:41:31.550 \rightarrow 00:41:34.175$  and the kinase domain for the males,

NOTE Confidence: 0.850281715393066

 $00{:}41{:}34{.}180 \dashrightarrow 00{:}41{:}36{.}120$  and so that's appear.

NOTE Confidence: 0.850281715393066

 $00:41:36.120 \longrightarrow 00:41:37.575$  This panel here.

NOTE Confidence: 0.850281715393066

00:41:37.580 --> 00:41:37.926 OK,

NOTE Confidence: 0.850281715393066

 $00:41:37.926 \longrightarrow 00:41:40.348$  so it's the mutant and non mutant

NOTE Confidence: 0.850281715393066

 $00{:}41{:}40{.}348 \dashrightarrow 00{:}41{:}42{.}715$  and then the variance of import

NOTE Confidence: 0.850281715393066

 $00:41:42.715 \longrightarrow 00:41:45.109$  also differed by sex for PK3R1

NOTE Confidence: 0.850281715393066

 $00{:}41{:}45{.}184 \dashrightarrow 00{:}41{:}47{.}620$  and so that's interesting in part

NOTE Confidence: 0.850281715393066

 $00:41:47.620 \longrightarrow 00:41:50.234$  because we know that the way in

NOTE Confidence: 0.850281715393066

 $00:41:50.234 \rightarrow 00:41:52.202$  which these areas are targeted by

NOTE Confidence: 0.850281715393066

 $00:41:52.202 \rightarrow 00:41:54.309$  various chemotherapies does differ.

NOTE Confidence: 0.850281715393066

 $00:41:54.310 \longrightarrow 00:41:56.718$  We looked in the literature an we

NOTE Confidence: 0.850281715393066

 $00:41:56.718 \rightarrow 00:41:59.359$  don't see too much reported honest.

- NOTE Confidence: 0.850281715393066
- 00:41:59.360 --> 00:42:01.968 We did find a paper by Dan Cahill
- NOTE Confidence: 0.850281715393066
- $00{:}42{:}01{.}968 \dashrightarrow 00{:}42{:}04{.}875$  at all at mass general and although
- NOTE Confidence: 0.850281715393066
- $00:42:04.875 \longrightarrow 00:42:07.530$  they didn't report it as such,
- NOTE Confidence: 0.850281715393066
- $00{:}42{:}07{.}530 \dashrightarrow 00{:}42{:}09{.}098$  they found something similar
- NOTE Confidence: 0.850281715393066
- $00{:}42{:}09{.}098 \dashrightarrow 00{:}42{:}11{.}450$  where the females tended to have.
- NOTE Confidence: 0.850281715393066
- $00{:}42{:}11.450 \dashrightarrow 00{:}42{:}14.803$  Variations in the he local domain and
- NOTE Confidence: 0.850281715393066
- $00:42:14.803 \rightarrow 00:42:18.788$  the males had them in the kinase domain,
- NOTE Confidence: 0.850281715393066
- $00:42:18.790 \longrightarrow 00:42:21.230$  and so as I said,
- NOTE Confidence: 0.850281715393066
- $00:42:21.230 \longrightarrow 00:42:23.182$  although both domains are
- NOTE Confidence: 0.850281715393066
- $00:42:23.182 \longrightarrow 00:42:25.134$  involved with glioma Genesis,
- NOTE Confidence: 0.850281715393066
- $00:42:25.140 \longrightarrow 00:42:27.585$  there is differential amounts of
- NOTE Confidence: 0.850281715393066
- 00:42:27.585 --> 00:42:30.030 potentiated by these two regions.
- NOTE Confidence: 0.850281715393066
- $00{:}42{:}30{.}030 \dashrightarrow 00{:}42{:}32{.}282$  And obviously there's different
- NOTE Confidence: 0.850281715393066
- $00{:}42{:}32.282 \dashrightarrow 00{:}42{:}34.534$  sensitivity to various treatment
- NOTE Confidence: 0.850281715393066
- $00:42:34.534 \longrightarrow 00:42:36.579$  types depending upon domain.
- NOTE Confidence: 0.850281715393066

 $00:42:36.580 \rightarrow 00:42:38.500$  So back to environmental exposure.

NOTE Confidence: 0.850281715393066

 $00:42:38.500 \rightarrow 00:42:40.705$  We have searched and not just our

NOTE Confidence: 0.850281715393066

00:42:40.705 --> 00:42:43.007 group of many groups have searched NOTE Confidence: 0.850281715393066

 $00:42:43.007 \rightarrow 00:42:45.581$  long and hard for environmental and

NOTE Confidence: 0.850281715393066

 $00{:}42{:}45{.}581 \dashrightarrow 00{:}42{:}47{.}688$  genetic risk factors for glioma.

NOTE Confidence: 0.850281715393066

00:42:47.690 --> 00:42:49.988 In terms of genetic risk factors,

NOTE Confidence: 0.879732668399811

 $00{:}42{:}49{.}990 \dashrightarrow 00{:}42{:}52{.}559$  we have found small numbers of families

NOTE Confidence: 0.879732668399811

 $00:42:52.559 \rightarrow 00:42:55.361$  with high risk but typically that does

NOTE Confidence: 0.879732668399811

 $00:42:55.361 \longrightarrow 00:42:57.809$  not relate to the general population

NOTE Confidence: 0.879732668399811

 $00{:}42{:}57{.}877 \dashrightarrow 00{:}43{:}00{.}037$  and so no genetic risk factors

NOTE Confidence: 0.879732668399811

 $00{:}43{:}00{.}037 \dashrightarrow 00{:}43{:}02{.}298$  really explain a large proportion of

NOTE Confidence: 0.879732668399811

 $00:43:02.298 \rightarrow 00:43:05.161$  inherited risk and other than high dose

NOTE Confidence: 0.879732668399811

00:43:05.161 -> 00:43:07.269 radiation to which not many people.

NOTE Confidence: 0.879732668399811

 $00:43:07.270 \longrightarrow 00:43:08.407$  Thankfully are exposed.

NOTE Confidence: 0.879732668399811

 $00{:}43{:}08{.}407 \dashrightarrow 00{:}43{:}11.060$  We really haven't found much of an

NOTE Confidence: 0.879732668399811

 $00:43:11.132 \rightarrow 00:43:12.653$  Association between environmental

- NOTE Confidence: 0.879732668399811
- $00:43:12.653 \longrightarrow 00:43:15.188$  risk factors in glioma risk.
- NOTE Confidence: 0.879732668399811
- 00:43:15.190 --> 00:43:17.830 There has been reported a fairly
- NOTE Confidence: 0.879732668399811
- 00:43:17.830 --> 00:43:19.590 consistent but low effect,
- NOTE Confidence: 0.879732668399811
- $00{:}43{:}19.590 \dashrightarrow 00{:}43{:}21.698$  an inverse Association with
- NOTE Confidence: 0.879732668399811
- 00:43:21.698 --> 00:43:23.279 history of allergy.
- NOTE Confidence: 0.879732668399811
- $00:43:23.280 \longrightarrow 00:43:24.736$  So the question comes,
- NOTE Confidence: 0.879732668399811
- $00:43:24.736 \rightarrow 00:43:26.556$  why haven't we found anything?
- NOTE Confidence: 0.879732668399811
- $00:43:26.560 \rightarrow 00:43:29.094$  Is it that there is no Association?
- NOTE Confidence: 0.879732668399811
- $00{:}43{:}29{.}100 \dashrightarrow 00{:}43{:}31{.}242$  Or is it basically statistical power
- NOTE Confidence: 0.879732668399811
- $00:43:31.242 \rightarrow 00:43:33.832$  that there's so few cases of glioma
- NOTE Confidence: 0.879732668399811
- $00:43:33.832 \rightarrow 00:43:36.380$  relative to other things we've looked at?
- NOTE Confidence: 0.879732668399811
- $00{:}43{:}36{.}380 \dashrightarrow 00{:}43{:}37{.}114$  For example,
- NOTE Confidence: 0.879732668399811
- $00:43:37.114 \longrightarrow 00:43:39.316$  I started my work with breast
- NOTE Confidence: 0.879732668399811
- $00:43:39.316 \longrightarrow 00:43:41.536$  cancer and even just using the
- NOTE Confidence: 0.879732668399811
- $00:43:41.536 \longrightarrow 00:43:43.654$  state of Connecticut as a base,
- NOTE Confidence: 0.879732668399811
00:43:43.660 - 00:43:45.380 you would have enough cases

NOTE Confidence: 0.879732668399811

 $00:43:45.380 \longrightarrow 00:43:47.670$  for a large study for glioma.

NOTE Confidence: 0.879732668399811

 $00:43:47.670 \longrightarrow 00:43:50.198$  That is not true and also likely a

NOTE Confidence: 0.879732668399811

 $00:43:50.198 \longrightarrow 00:43:53.196$  lot of the exposures that we think

NOTE Confidence: 0.879732668399811

 $00:43:53.196 \longrightarrow 00:43:55.940$  are causing risk are themselves rare.

NOTE Confidence: 0.879732668399811

 $00:43:55.940 \longrightarrow 00:43:58.460$  So one of the things that people

NOTE Confidence: 0.879732668399811

00:43:58.460 -> 00:44:00.460 have been thinking about doing,

NOTE Confidence: 0.879732668399811

 $00:44:00.460 \rightarrow 00:44:03.476$  is there another way to do this now?

NOTE Confidence: 0.879732668399811

 $00{:}44{:}03{.}480 \dashrightarrow 00{:}44{:}06{.}301$  So now that we have these mutational

NOTE Confidence: 0.879732668399811

 $00{:}44{:}06{.}301 \dashrightarrow 00{:}44{:}08{.}861$  signatures that the are listed in

NOTE Confidence: 0.879732668399811

00:44:08.861 --> 00:44:10.986 the Catalogue of Somatic mutations

NOTE Confidence: 0.879732668399811

00:44:10.986 --> 00:44:13.348 and cancer or cosmic can use that

NOTE Confidence: 0.879732668399811

 $00:44:13.348 \longrightarrow 00:44:16.005$  as a way to match up to exposure,

NOTE Confidence: 0.879732668399811

 $00{:}44{:}16.005 \dashrightarrow 00{:}44{:}18.030$  particularly if you have previously

NOTE Confidence: 0.879732668399811

 $00{:}44{:}18.030 \dashrightarrow 00{:}44{:}19.555$  obtained environmental or other

NOTE Confidence: 0.879732668399811

00:44:19.555 --> 00:44:21.195 exposure history in the patients.

- NOTE Confidence: 0.879732668399811
- $00:44:21.200 \longrightarrow 00:44:23.594$  So we did that here with the
- NOTE Confidence: 0.879732668399811
- $00:44:23.594 \longrightarrow 00:44:25.719$  1100 cases that we mentioned,
- NOTE Confidence: 0.879732668399811
- 00:44:25.720 --> 00:44:27.268 we group Jack Sonic.
- NOTE Confidence: 0.879732668399811
- $00:44:27.268 \longrightarrow 00:44:29.590$  SNV and tried to match him
- NOTE Confidence: 0.879732668399811
- $00:44:29.673 \longrightarrow 00:44:31.647$  up to what is in cosmic,
- NOTE Confidence: 0.879732668399811
- $00{:}44{:}31{.}650 \dashrightarrow 00{:}44{:}33{.}974$  and so you know that the cosmic
- NOTE Confidence: 0.879732668399811
- $00:44:33.974 \rightarrow 00:44:35.640$  catalog is rapidly changing.
- NOTE Confidence: 0.879732668399811
- $00:44:35.640 \rightarrow 00:44:37.806$  New things are always being added,
- NOTE Confidence: 0.879732668399811
- $00{:}44{:}37{.}810 \dashrightarrow 00{:}44{:}41{.}068$  but we looked at what existed at this point,
- NOTE Confidence: 0.879732668399811
- $00{:}44{:}41.070 \dashrightarrow 00{:}44{:}43.080$  and obviously they have previously found
- NOTE Confidence: 0.879732668399811
- $00:44:43.080 \rightarrow 00:44:45.594$  a match up over environmental exposure to
- NOTE Confidence: 0.879732668399811
- 00:44:45.594 --> 00:44:48.670 signatures not only in head and neck cancer,
- NOTE Confidence: 0.879732668399811
- $00{:}44{:}48.670 \dashrightarrow 00{:}44{:}50.480$  but smoking and lung cancer,
- NOTE Confidence: 0.879732668399811
- $00:44:50.480 \longrightarrow 00:44:51.324$  UV exposure,
- NOTE Confidence: 0.879732668399811
- $00{:}44{:}51{.}324 \dashrightarrow 00{:}44{:}54{.}700$  and so we looked at that for glioma.
- NOTE Confidence: 0.879732668399811

- 00:44:54.700 --> 00:44:56.068 And so again,
- NOTE Confidence: 0.879732668399811
- 00:44:56.068 --> 00:44:58.348 here's our slide here again,
- NOTE Confidence: 0.879732668399811
- 00:44:58.350 --> 00:45:00.174 broken into IDH Mutant,
- NOTE Confidence: 0.879732668399811
- $00:45:00.174 \rightarrow 00:45:02.910$  which is the top row IDH,
- NOTE Confidence: 0.879732668399811
- $00:45:02.910 \rightarrow 00:45:05.790$  Wildtype bottom row and then females
- NOTE Confidence: 0.879732668399811
- $00{:}45{:}05{.}790 \dashrightarrow 00{:}45{:}08{.}598$  or first column mails or second
- NOTE Confidence: 0.879732668399811
- $00{:}45{:}08.598 \dashrightarrow 00{:}45{:}11.567$  column with each of these bar charts
- NOTE Confidence: 0.879732668399811
- $00{:}45{:}11.567 \dashrightarrow 00{:}45{:}14.696$  relates to is the proportion of our
- NOTE Confidence: 0.879732668399811
- $00{:}45{:}14.696 \dashrightarrow 00{:}45{:}18.463$  cases for whom the majority seem to be
- NOTE Confidence: 0.879732668399811
- $00{:}45{:}18{.}463 \dashrightarrow 00{:}45{:}21{.}270$  associated with a certain signature.
- NOTE Confidence: 0.879732668399811
- $00{:}45{:}21{.}270 \dashrightarrow 00{:}45{:}23{.}545$  And the overall news is a little
- NOTE Confidence: 0.879732668399811
- $00{:}45{:}23.545 \dashrightarrow 00{:}45{:}25.853$  bit depressing in the sense that
- NOTE Confidence: 0.879732668399811
- $00:45:25.853 \rightarrow 00:45:27.541$  the primary molecular signature
- NOTE Confidence: 0.879732668399811
- $00:45:27.541 \rightarrow 00:45:30.179$  identified was age related mutagenesis.
- NOTE Confidence: 0.879732668399811
- $00:45:30.180 \longrightarrow 00:45:32.210$  Basically the older you get,
- NOTE Confidence: 0.879732668399811
- $00:45:32.210 \longrightarrow 00:45:34.640$  the more at risk you are,

NOTE Confidence: 0.879732668399811

 $00:45:34.640 \longrightarrow 00:45:37.475$  but we did find one thing that

NOTE Confidence: 0.879732668399811

00:45:37.475 - 00:45:38.690 was quite interesting,

NOTE Confidence: 0.879732668399811

 $00:45:38.690 \rightarrow 00:45:40.886$  particularly in light of their such

NOTE Confidence: 0.879732668399811

 $00:45:40.886 \rightarrow 00:45:42.842$  a positive risk factors identified

NOTE Confidence: 0.879732668399811

 $00:45:42.842 \rightarrow 00:45:45.410$  for glioma and that was occupational

NOTE Confidence: 0.879732668399811

 $00{:}45{:}45{.}410 \dashrightarrow 00{:}45{:}47{.}998$  exposure to something called Halo alkanes.

NOTE Confidence: 0.879732668399811

 $00{:}45{:}48.000 \dashrightarrow 00{:}45{:}50.030$  Pretty much true across whether

NOTE Confidence: 0.879732668399811

 $00:45:50.030 \longrightarrow 00:45:52.060$  you are male or female.

NOTE Confidence: 0.879732668399811

 $00:45:52.060 \rightarrow 00:45:53.970$  And whether you were IDH,

NOTE Confidence: 0.879732668399811

 $00:45:53.970 \longrightarrow 00:45:55.026$  mutant or not,

NOTE Confidence: 0.879732668399811

 $00{:}45{:}55{.}026 \dashrightarrow 00{:}45{:}57{.}490$  we did find a little greater rate

NOTE Confidence: 0.879732668399811

 $00{:}45{:}57{.}566 \dashrightarrow 00{:}45{:}59{.}810$  of the signature showing up in

NOTE Confidence: 0.879732668399811

 $00{:}45{:}59{.}810 \dashrightarrow 00{:}46{:}01{.}970$  the males versus the females.

NOTE Confidence: 0.879732668399811

 $00{:}46{:}01{.}970 \dashrightarrow 00{:}46{:}04{.}392$  But we certainly saw them in both

NOTE Confidence: 0.879732668399811

 $00{:}46{:}04{.}392 \dashrightarrow 00{:}46{:}07{.}043$  and then we also saw which we

NOTE Confidence: 0.879732668399811

 $00:46:07.043 \rightarrow 00:46:09.347$  haven't quite figured out how to

NOTE Confidence: 0.836727201938629

 $00:46:09.427 \rightarrow 00:46:12.435$  explain yet. These UV light signatures an

NOTE Confidence: 0.836727201938629

00:46:12.435 --> 00:46:14.979 it's interesting because glioma has been

NOTE Confidence: 0.836727201938629

 $00{:}46{:}14.979 \dashrightarrow 00{:}46{:}17.325$  associated in the number of instances

NOTE Confidence: 0.836727201938629

 $00{:}46{:}17.325 \dashrightarrow 00{:}46{:}19.866$  with Melanoma and also with the B RAF.

NOTE Confidence: 0.836727201938629

 $00:46:19.870 \rightarrow 00:46:22.998$  So we're trying to sort out whether that.

NOTE Confidence: 0.836727201938629

00:46:23.000 --> 00:46:24.729 Has anything to do with why we're

NOTE Confidence: 0.836727201938629

 $00:46:24.729 \rightarrow 00:46:26.508$  just seeing some of those signatures?

NOTE Confidence: 0.836727201938629

 $00{:}46{:}26{.}510 \dashrightarrow 00{:}46{:}29{.}919$  So hello, alkanes are basically used for

NOTE Confidence: 0.836727201938629

 $00:46:29.919 \rightarrow 00:46:33.089$  many industrial and day-to-day purposes.

NOTE Confidence: 0.836727201938629

 $00{:}46{:}33.090 \dashrightarrow 00{:}46{:}35.496$  Of interest there seen in refrigerants,

NOTE Confidence: 0.836727201938629

 $00:46:35.500 \rightarrow 00:46:37.300$  fire extinguishers, flame retardants,

NOTE Confidence: 0.836727201938629

 $00:46:37.300 \rightarrow 00:46:40.509$  and we thought this was very interesting

NOTE Confidence: 0.836727201938629

 $00{:}46{:}40.509 \dashrightarrow 00{:}46{:}43.125$  because there's always sort of been

NOTE Confidence: 0.836727201938629

 $00:46:43.125 \longrightarrow 00:46:45.670$  this theory that in some of these.

NOTE Confidence: 0.836727201938629

00:46:45.670 --> 00:46:47.366 Occupations including for firemen

NOTE Confidence: 0.836727201938629

 $00{:}46{:}47.366 \dashrightarrow 00{:}46{:}49.910$  and that has been reported that

NOTE Confidence: 0.836727201938629

 $00:46:49.976 \longrightarrow 00:46:52.384$  there is an increased risk of glioma,

NOTE Confidence: 0.836727201938629

 $00:46:52.390 \longrightarrow 00:46:55.120$  and so, whether or not this ties

NOTE Confidence: 0.836727201938629

 $00:46:55.120 \rightarrow 00:46:57.520$  things together or not is unclear,

NOTE Confidence: 0.836727201938629

 $00:46:57.520 \longrightarrow 00:47:00.022$  so the signature was basically developed

NOTE Confidence: 0.836727201938629

 $00{:}47{:}00{.}022 \dashrightarrow 00{:}47{:}02{.}489$  by looking at cholangio carcinoma in

NOTE Confidence: 0.836727201938629

 $00:47:02.489 \rightarrow 00:47:05.023$  a group of workers that were exposed,

NOTE Confidence: 0.836727201938629

 $00:47:05.030 \rightarrow 00:47:07.412$  known, exposed to hello Alkins in

NOTE Confidence: 0.836727201938629

 $00{:}47{:}07{.}412 \dashrightarrow 00{:}47{:}09{.}832$  Japan and so essentially they had

NOTE Confidence: 0.836727201938629

 $00:47:09.832 \longrightarrow 00:47:11.737$  111 workers that were exposed.

NOTE Confidence: 0.836727201938629

 $00:47:11.740 \longrightarrow 00:47:12.520$  17 developed.

NOTE Confidence: 0.836727201938629

 $00:47:12.520 \rightarrow 00:47:16.140$  Would you all know to be a pretty rare?

NOTE Confidence: 0.836727201938629

 $00:47:16.140 \longrightarrow 00:47:16.465$  Cancer,

NOTE Confidence: 0.836727201938629

 $00{:}47{:}16.465 \dashrightarrow 00{:}47{:}19.065$  so it was quite unusual that this number

NOTE Confidence: 0.836727201938629

 $00{:}47{:}19.065 \dashrightarrow 00{:}47{:}21.630$  of individuals was diagnosed with it.

NOTE Confidence: 0.836727201938629

00:47:21.630 --> 00:47:23.688 They all were working in printing

NOTE Confidence: 0.836727201938629

 $00:47:23.688 \rightarrow 00:47:25.910$  companies and they all were known

NOTE Confidence: 0.836727201938629

 $00{:}47{:}25{.}910$  -->  $00{:}47{:}28{.}262$  to have occupational exposure and so

NOTE Confidence: 0.836727201938629

 $00:47:28.262 \rightarrow 00:47:30.859$  essentially what they did was they took

NOTE Confidence: 0.836727201938629

 $00:47:30.859 \longrightarrow 00:47:32.604$  the tumors from these individuals,

NOTE Confidence: 0.836727201938629

 $00{:}47{:}32.610 \dashrightarrow 00{:}47{:}34.474$  looked at the molecular.

NOTE Confidence: 0.836727201938629

 $00:47:34.474 \rightarrow 00:47:36.804$  Pattern and developed this signature.

NOTE Confidence: 0.836727201938629

 $00{:}47{:}36{.}810 \dashrightarrow 00{:}47{:}39{.}462$  So that's essentially how that the

NOTE Confidence: 0.836727201938629

 $00{:}47{:}39{.}462 \dashrightarrow 00{:}47{:}41{.}230$  signature was initially identified,

NOTE Confidence: 0.836727201938629

 $00:47:41.230 \longrightarrow 00:47:43.876$  and so that's what we're seeing.

NOTE Confidence: 0.836727201938629

 $00{:}47{:}43.880 \dashrightarrow 00{:}47{:}45.536$  Basically in our data.

NOTE Confidence: 0.836727201938629

 $00{:}47{:}45{.}536 \dashrightarrow 00{:}47{:}48{.}020$  So conclusions here that the majority

NOTE Confidence: 0.836727201938629

 $00{:}47{:}48.093 \dashrightarrow 00{:}47{:}50.865$  of cancer causing mutations in these

NOTE Confidence: 0.836727201938629

 $00:47:50.865 \rightarrow 00:47:53.217$  gliomas we're seeing primarily as

NOTE Confidence: 0.836727201938629

 $00:47:53.217 \longrightarrow 00:47:54.929$  a consequence of endogenous,

NOTE Confidence: 0.836727201938629

 $00:47:54.930 \rightarrow 00:47:57.140$  rather than actual, exogenous exposures.

NOTE Confidence: 0.836727201938629

 $00:47:57.140 \longrightarrow 00:47:59.864$  We did think was interesting that

NOTE Confidence: 0.836727201938629

 $00{:}47{:}59{.}864 \dashrightarrow 00{:}48{:}03{.}037$  different domains of jeans in the P3K

NOTE Confidence: 0.836727201938629

 $00:48:03.037 \rightarrow 00:48:06.005$  pathway were different for males and females.

NOTE Confidence: 0.836727201938629

00:48:06.010 --> 00:48:08.460 For those of us that have searched

NOTE Confidence: 0.836727201938629

 $00:48:08.460 \longrightarrow 00:48:11.117$  long and hard for some of these

NOTE Confidence: 0.836727201938629

00:48:11.117 --> 00:48:12.649 risk factors for glioma,

NOTE Confidence: 0.836727201938629

 $00:48:12.650 \rightarrow 00:48:15.240$  we are excited that at least potentially,

NOTE Confidence: 0.836727201938629

 $00:48:15.240 \longrightarrow 00:48:17.394$  there's a new means to try

NOTE Confidence: 0.836727201938629

 $00:48:17.394 \rightarrow 00:48:19.290$  and identify even if rare,

NOTE Confidence: 0.836727201938629

 $00:48:19.290 \longrightarrow 00:48:20.806$  these environmental risk factors

NOTE Confidence: 0.836727201938629

 $00{:}48{:}20.806 \dashrightarrow 00{:}48{:}23.806$  and it's sort of a whole new aspect

NOTE Confidence: 0.836727201938629

 $00{:}48{:}23.806 \dashrightarrow 00{:}48{:}26.088$  of glioma that were looking at so

NOTE Confidence: 0.836727201938629

 $00{:}48{:}26.088 \dashrightarrow 00{:}48{:}28.149$  some of our future directions.

NOTE Confidence: 0.836727201938629

 $00{:}48{:}28{.}150 \dashrightarrow 00{:}48{:}30{.}400$  We're looking now to partner with

NOTE Confidence: 0.836727201938629

 $00{:}48{:}30{.}400 \dashrightarrow 00{:}48{:}32{.}675$  colleagues who have worked with us

NOTE Confidence: 0.836727201938629

 $00:48:32.675 \rightarrow 00:48:34.787$  both in the meningioma consortia man,

NOTE Confidence: 0.836727201938629

 $00{:}48{:}34{.}790 \dashrightarrow 00{:}48{:}36{.}274$  the Glioma international Case

NOTE Confidence: 0.836727201938629

00:48:36.274 --> 00:48:37.016 Control Consortium.

NOTE Confidence: 0.836727201938629

 $00{:}48{:}37{.}020 \dashrightarrow 00{:}48{:}39{.}462$  And we also in our international

NOTE Confidence: 0.836727201938629

 $00:48:39.462 \longrightarrow 00:48:41.090$  low grade glioma registry.

NOTE Confidence: 0.836727201938629

 $00:48:41.090 \longrightarrow 00:48:43.400$  Looking at cohorts in which we

NOTE Confidence: 0.836727201938629

00:48:43.400 --> 00:48:45.570 have a good occupational history.

NOTE Confidence: 0.836727201938629

00:48:45.570 --> 00:48:48.006 So the San Francisco Bay Area

NOTE Confidence: 0.836727201938629

00:48:48.006 --> 00:48:49.224 Adult Glioma study,

NOTE Confidence: 0.836727201938629

 $00:48:49.230 \longrightarrow 00:48:51.666$  which is led by Margaret Wrench

NOTE Confidence: 0.836727201938629

00:48:51.666 --> 00:48:52.884 and John Winky,

NOTE Confidence: 0.836727201938629

 $00:48:52.890 \rightarrow 00:48:54.518$  they collected extremely detailed

NOTE Confidence: 0.836727201938629

 $00:48:54.518 \rightarrow 00:48:56.553$  occupational history for their cohort,

NOTE Confidence: 0.836727201938629

 $00{:}48{:}56{.}560 \dashrightarrow 00{:}48{:}58{.}996$  and they have all the tumors.

NOTE Confidence: 0.836727201938629

 $00{:}48{:}59{.}000 \dashrightarrow 00{:}49{:}02{.}042$  So we're going to try and go back and

NOTE Confidence: 0.836727201938629

 $00:49:02.042 \rightarrow 00:49:04.838$  Geno type those tumors and see if

- NOTE Confidence: 0.836727201938629
- $00:49:04.838 \rightarrow 00:49:07.550$  we can confirm these associations,
- NOTE Confidence: 0.836727201938629
- $00:49:07.550 \rightarrow 00:49:09.870$  which they found with firefighters.
- NOTE Confidence: 0.836727201938629
- $00{:}49{:}09{.}870 \dashrightarrow 00{:}49{:}10.624$  And glioma.
- NOTE Confidence: 0.836727201938629
- $00:49:10.624 \rightarrow 00:49:14.090$  And also they found it with painters as well.
- NOTE Confidence: 0.836727201938629
- $00{:}49{:}14.090 \dashrightarrow 00{:}49{:}16.981$  And so we are also collecting glioma
- NOTE Confidence: 0.836727201938629
- $00:49:16.981 \rightarrow 00:49:18.638$  patients with occupational histories
- NOTE Confidence: 0.836727201938629
- $00:49:18.638 \rightarrow 00:49:21.761$  and just sort of throwing it out to people.
- NOTE Confidence: 0.836727201938629
- 00:49:21.770 --> 00:49:24.386 If you're aware of any firefighters
- NOTE Confidence: 0.836727201938629
- $00{:}49{:}24{.}386 \dashrightarrow 00{:}49{:}26{.}494$  or similar occupied individuals with
- NOTE Confidence: 0.836727201938629
- $00{:}49{:}26{.}494 \dashrightarrow 00{:}49{:}28{.}587$  glioma would love to try and get
- NOTE Confidence: 0.836727201938629
- $00:49:28.587 \longrightarrow 00:49:29.185$  a cohort
- NOTE Confidence: 0.812601149082184
- $00{:}49{:}29{.}254 \dashrightarrow 00{:}49{:}31{.}585$  together. The other thing that was
- NOTE Confidence: 0.812601149082184
- $00{:}49{:}31{.}585 \dashrightarrow 00{:}49{:}34{.}449$  just sort of luck this past semester.
- NOTE Confidence: 0.812601149082184
- $00{:}49{:}34{.}450 \dashrightarrow 00{:}49{:}37{.}124$  So I teach over at the school,
- NOTE Confidence: 0.812601149082184
- $00:49:37.130 \longrightarrow 00:49:39.874$  public health and everything has been remote.
- NOTE Confidence: 0.812601149082184

 $00:49:39.880 \longrightarrow 00:49:42.922$  And so as I was meeting via zoom with

NOTE Confidence: 0.812601149082184

 $00:49:42.922 \rightarrow 00:49:46.404$  one of my students for her final project,

NOTE Confidence: 0.812601149082184

 $00:49:46.410 \longrightarrow 00:49:48.648$  she revealed that she was actually

NOTE Confidence: 0.812601149082184

 $00:49:48.648 \rightarrow 00:49:50.589$  the principle project director for

NOTE Confidence: 0.812601149082184

 $00:49:50.589 \rightarrow 00:49:52.549$  the Firefighters Cancer Cohort study.

NOTE Confidence: 0.812601149082184

 $00:49:52.550 \longrightarrow 00:49:54.860$  So we're also hoping to parano.

NOTE Confidence: 0.812601149082184

 $00:49:54.860 \rightarrow 00:49:57.348$  NIH is a big directive to try and

NOTE Confidence: 0.812601149082184

 $00{:}49{:}57{.}348 \dashrightarrow 00{:}49{:}59{.}075$  look further at environmental

NOTE Confidence: 0.812601149082184

 $00:49:59.075 \longrightarrow 00:50:00.620$  exposures and cancer,

NOTE Confidence: 0.812601149082184

 $00:50:00.620 \rightarrow 00:50:03.420$  so we're hoping that we can partner with

NOTE Confidence: 0.812601149082184

 $00{:}50{:}03{.}420 \dashrightarrow 00{:}50{:}06{.}758$  some of these folks to look at individuals,

NOTE Confidence: 0.812601149082184

 $00:50:06.760 \longrightarrow 00:50:08.720$  either living or dead that

NOTE Confidence: 0.812601149082184

 $00:50:08.720 \longrightarrow 00:50:09.896$  may have undiagnosed.

NOTE Confidence: 0.812601149082184

 $00:50:09.900 \rightarrow 00:50:13.148$  With glioma that we now have this exposure.

NOTE Confidence: 0.812601149082184

 $00:50:13.150 \longrightarrow 00:50:15.649$  So thank you all for your time.

NOTE Confidence: 0.812601149082184

00:50:15.650 --> 00:50:18.149 I wanted to also thank Jeff Townsend,

- NOTE Confidence: 0.812601149082184
- 00:50:18.150 --> 00:50:19.212 Vinston, Canna Terra,
- NOTE Confidence: 0.812601149082184
- $00{:}50{:}19{.}212 \dashrightarrow 00{:}50{:}23{.}152$  who was a postdoc in Jeffs lab but now as an
- NOTE Confidence: 0.812601149082184
- $00:50:23.152 \rightarrow 00:50:25.650$  assistant professor of biology up the road,
- NOTE Confidence: 0.812601149082184
- $00{:}50{:}25{.}650 \dashrightarrow 00{:}50{:}27{.}375$  a little bit of Emmanuel
- NOTE Confidence: 0.812601149082184
- 00:50:27.375 -> 00:50:29.929 College and I have to thank him.
- NOTE Confidence: 0.812601149082184
- $00:50:29.930 \longrightarrow 00:50:31.710$  He made all the beautiful
- NOTE Confidence: 0.812601149082184
- 00:50:31.710 --> 00:50:33.134 pictures an Steven Gaffney,
- NOTE Confidence: 0.812601149082184
- $00:50:33.140 \longrightarrow 00:50:35.276$  who also works in Jeff Slab.
- NOTE Confidence: 0.812601149082184
- $00:50:35.280 \longrightarrow 00:50:36.678$  Thank the various.
- NOTE Confidence: 0.812601149082184
- 00:50:36.678 --> 00:50:38.076 Brain tumor associations,
- NOTE Confidence: 0.812601149082184
- $00:50:38.080 \rightarrow 00:50:39.745$  including the ABCA in the
- NOTE Confidence: 0.812601149082184
- 00:50:39.745 --> 00:50:41.830 NBTS as well as Luglio Anna,
- NOTE Confidence: 0.812601149082184
- $00{:}50{:}41.830 \dashrightarrow 00{:}50{:}44.050$ a Dutch group called Stop Brain
- NOTE Confidence: 0.812601149082184
- $00{:}50{:}44.050 \dashrightarrow 00{:}50{:}46.346$  Tumor for their support and then
- NOTE Confidence: 0.812601149082184
- $00{:}50{:}46{.}346 \dashrightarrow 00{:}50{:}48{.}566$  also thank you for Doctor Rolled
- NOTE Confidence: 0.812601149082184

 $00:50:48.566 \rightarrow 00:50:50.492$  their hacking the Glass consortium

NOTE Confidence: 0.812601149082184

 $00{:}50{:}50{.}492 \dashrightarrow 00{:}50{:}53{.}082$  who allowed us access to the data.

NOTE Confidence: 0.812601149082184

 $00:50:53.090 \rightarrow 00:50:56.138$  So happy to take any questions.

NOTE Confidence: 0.865883529186249

 $00:50:56.860 \rightarrow 00:50:58.102$  Elizabeth, thank you.

NOTE Confidence: 0.865883529186249

 $00{:}50{:}58{.}102 \dashrightarrow 00{:}51{:}01{.}000$  That was a terrific summary of your

NOTE Confidence: 0.865883529186249

 $00{:}51{:}01{.}080 \dashrightarrow 00{:}51{:}03{.}258$  work and obviously will open it

NOTE Confidence: 0.865883529186249

 $00:51:03.258 \rightarrow 00:51:05.808$  up to questions on the chat line.

NOTE Confidence: 0.865883529186249

 $00{:}51{:}05{.}810 \dashrightarrow 00{:}51{:}07{.}066$  But let me ask.

NOTE Confidence: 0.865883529186249

00:51:07.066 --> 00:51:08.950 I found it interesting the the

NOTE Confidence: 0.865883529186249

 $00:51:09.022 \dashrightarrow 00:51:11.037$  observation I guess from Asia

NOTE Confidence: 0.865883529186249

 $00{:}51{:}11{.}037 \dashrightarrow 00{:}51{:}13{.}052$  about the Association of Halo

NOTE Confidence: 0.865883529186249

 $00:51:13.123 \rightarrow 00:51:15.310$  alkanes with cholangiocarcinoma.

NOTE Confidence: 0.865883529186249

00:51:15.310 --> 00:51:16.842 As you may know,

NOTE Confidence: 0.865883529186249

 $00:51:16.842 \longrightarrow 00:51:18.374$  there's there's a biologic

NOTE Confidence: 0.865883529186249

 $00:51:18.374 \rightarrow 00:51:20.010$  difference between intrahepatic,

NOTE Confidence: 0.865883529186249

 $00:51:20.010 \rightarrow 00:51:22.054$  an extra paddock cholangio,

- NOTE Confidence: 0.865883529186249
- $00:51:22.054 \rightarrow 00:51:24.609$  where extra panic actually gave
- NOTE Confidence: 0.865883529186249
- $00{:}51{:}24.609 \dashrightarrow 00{:}51{:}27.094$  IDH mutations but insured don't
- NOTE Confidence: 0.865883529186249
- $00:51:27.094 \rightarrow 00:51:29.920$  wear the cases that they found
- NOTE Confidence: 0.865883529186249
- $00:51:30.004 \rightarrow 00:51:32.356$  in Asia with a extra paddock.
- NOTE Confidence: 0.865883529186249
- 00:51:32.360 --> 00:51:32.640 You
- NOTE Confidence: 0.871688604354858
- $00{:}51{:}32{.}640 \dashrightarrow 00{:}51{:}34{.}904$  know, I don't know the answer to that.
- NOTE Confidence: 0.871688604354858
- 00:51:34.910 --> 00:51:36.898 I gave a similar talk at UCSF
- NOTE Confidence: 0.871688604354858
- $00:51:36.898 \rightarrow 00:51:38.589$  and they mentioned this as well,
- NOTE Confidence: 0.871688604354858
- $00{:}51{:}38{.}590 \dashrightarrow 00{:}51{:}40{.}042$  so we're trying to gain access
- NOTE Confidence: 0.871688604354858
- $00:51:40.042 \longrightarrow 00:51:41.700$  to some of that information,
- NOTE Confidence: 0.871688604354858
- 00:51:41.700 --> 00:51:43.398 but I don't know at present.
- NOTE Confidence: 0.859068708760398
- $00{:}51{:}44{.}570 \dashrightarrow 00{:}51{:}47{.}586$  And then. With regard to the finding of
- NOTE Confidence: 0.859068708760398
- $00:51:47.586 \longrightarrow 00:51:49.674$  the potential differential in mutations
- NOTE Confidence: 0.859068708760398
- $00{:}51{:}49{.}674 \dashrightarrow 00{:}51{:}52{.}970$  within pick three CA by gender by sex,
- NOTE Confidence: 0.859068708760398
- $00:51:52.970 \longrightarrow 00:51:54.515$  is there an understanding of
- NOTE Confidence: 0.859068708760398

00:51:54.515 --> 00:51:56.439 why those two domains would be

NOTE Confidence: 0.859068708760398

 $00{:}51{:}56{.}439 \dashrightarrow 00{:}51{:}58{.}049$  different between men and women?

NOTE Confidence: 0.859068708760398

00:51:58.050 --> 00:51:59.378 No, and you know,

NOTE Confidence: 0.859068708760398

 $00:51:59.378 \longrightarrow 00:52:01.530$  we started to look at that a

NOTE Confidence: 0.852207005023956

 $00{:}52{:}01{.}530 \dashrightarrow 00{:}52{:}03{.}115$  little bit and we collaborate

NOTE Confidence: 0.852207005023956

 $00{:}52{:}03.115 \dashrightarrow 00{:}52{:}04.700$  a bit with Dan Cahill.

NOTE Confidence: 0.852207005023956

00:52:04.700 --> 00:52:06.566 As I mentioned up at mass

NOTE Confidence: 0.852207005023956

 $00:52:06.566 \longrightarrow 00:52:08.509$  general so we don't know yet,

NOTE Confidence: 0.852207005023956

 $00{:}52{:}08{.}510$  -->  $00{:}52{:}10{.}868$  but he's going to try to take a look

NOTE Confidence: 0.852207005023956

 $00{:}52{:}10.868 \dashrightarrow 00{:}52{:}13.074$  into that he he presented the data

NOTE Confidence: 0.852207005023956

00:52:13.074 --> 00:52:15.160 but didn't note the differences,

NOTE Confidence: 0.852207005023956

 $00:52:15.160 \longrightarrow 00:52:17.246$  so he's going to try to take

NOTE Confidence: 0.852207005023956

 $00{:}52{:}17.246 \dashrightarrow 00{:}52{:}19.290$  a look and see what that.

NOTE Confidence: 0.852207005023956

 $00{:}52{:}19{.}290 \dashrightarrow 00{:}52{:}20{.}160$  Might entail.

NOTE Confidence: 0.855117380619049

 $00:52:20.760 \longrightarrow 00:52:22.510$  And then my last question,

NOTE Confidence: 0.855117380619049

 $00:52:22.510 \rightarrow 00:52:24.869$  and this is gonna show my naivete

- NOTE Confidence: 0.855117380619049
- $00:52:24.869 \rightarrow 00:52:26.360$  and understanding brain tumors.
- NOTE Confidence: 0.855117380619049
- $00:52:26.360 \longrightarrow 00:52:28.385$  But instead of the Natural
- NOTE Confidence: 0.855117380619049
- $00:52:28.385 \longrightarrow 00:52:30.410$  History of the low grades.
- NOTE Confidence: 0.855117380619049
- $00:52:30.410 \longrightarrow 00:52:33.380$  Is there an evolution of the
- NOTE Confidence: 0.855117380619049
- $00:52:33.380 \longrightarrow 00:52:35.944$  semantic events such that they
- NOTE Confidence: 0.855117380619049
- 00:52:35.944 --> 00:52:38.389 look more like high grades?
- NOTE Confidence: 0.854550182819366
- $00:52:38.400 \longrightarrow 00:52:39.366$  So it depends.
- NOTE Confidence: 0.854550182819366
- $00:52:39.366 \rightarrow 00:52:40.976$  They generally remain quite different.
- NOTE Confidence: 0.854550182819366
- $00:52:40.980 \rightarrow 00:52:42.995$  The IDH mutation stays constant
- NOTE Confidence: 0.854550182819366
- 00:52:42.995 --> 00:52:45.359 throughout and so that's sort of
- NOTE Confidence: 0.854550182819366
- $00:52:45.359 \rightarrow 00:52:47.298$  been one of the issues is what
- NOTE Confidence: 0.854550182819366
- $00:52:47.298 \longrightarrow 00:52:49.282$  you show up to the party with
- NOTE Confidence: 0.854550182819366
- $00:52:49.282 \rightarrow 00:52:51.256$  tends to be what you stay within.
- NOTE Confidence: 0.854550182819366
- $00{:}52{:}51{.}256 \dashrightarrow 00{:}52{:}53{.}104$  That makes it a little bit
- NOTE Confidence: 0.854550182819366
- $00:52:53.104 \longrightarrow 00:52:54.499$  different to manage them.
- NOTE Confidence: 0.854550182819366

 $00:52:54.500 \longrightarrow 00:52:56.607$  We didn't found find in some of

NOTE Confidence: 0.854550182819366

 $00{:}52{:}56{.}607 \dashrightarrow 00{:}52{:}58{.}230$  the glass consortium work that

NOTE Confidence: 0.854550182819366

 $00{:}52{:}58{.}230 \dashrightarrow 00{:}53{:}00{.}210$  we've looked at that really things

NOTE Confidence: 0.854550182819366

 $00:53:00.210 \rightarrow 00:53:01.897$  changed that much whether you

NOTE Confidence: 0.854550182819366

 $00{:}53{:}01{.}897 \dashrightarrow 00{:}53{:}03{.}512$  gave them treatment or whether

NOTE Confidence: 0.854550182819366

00:53:03.512 --> 00:53:05.164 you didn't give them treatment.

NOTE Confidence: 0.854550182819366

00:53:05.164 --> 00:53:06.874 Is a little bit disheartening,

NOTE Confidence: 0.854550182819366

 $00:53:06.880 \longrightarrow 00:53:09.640$  but we're going to try to look a

NOTE Confidence: 0.841290950775146

 $00:53:09.640 \longrightarrow 00:53:11.360$  little bit further at that.

NOTE Confidence: 0.841290950775146

00:53:11.360 --> 00:53:12.704 Yeah, yeah, you know,

NOTE Confidence: 0.841290950775146

00:53:12.704 --> 00:53:14.720 judging by the way you describe

NOTE Confidence: 0.841290950775146

00:53:14.786 --> 00:53:16.880 for the presence of Halo alkanes,

NOTE Confidence: 0.841290950775146

 $00:53:16.880 \longrightarrow 00:53:18.712$  you could imagine they

NOTE Confidence: 0.841290950775146

 $00:53:18.712 \longrightarrow 00:53:20.544$  may be more ubiquitous.

NOTE Confidence: 0.841290950775146

 $00:53:20.550 \rightarrow 00:53:22.488$  In our environment than we might

NOTE Confidence: 0.841290950775146

 $00:53:22.488 \rightarrow 00:53:23.457$  otherwise appreciate given

- NOTE Confidence: 0.841290950775146
- $00{:}53{:}23{.}457 \dashrightarrow 00{:}53{:}24{.}957$  all the things they are in
- NOTE Confidence: 0.846849322319031
- $00:53:24.960 \longrightarrow 00:53:26.136$  absolutely and it doesn't
- NOTE Confidence: 0.846849322319031
- $00:53:26.136 \rightarrow 00:53:27.900$  have to just relate to glioma.
- NOTE Confidence: 0.846849322319031
- 00:53:27.900 --> 00:53:29.365 You know could relate to
- NOTE Confidence: 0.846849322319031
- $00:53:29.365 \longrightarrow 00:53:31.930$  lots of different things so.
- NOTE Confidence: 0.83347088098526
- 00:53:31.930 --> 00:53:33.112 Well, very interesting.
- NOTE Confidence: 0.83347088098526
- 00:53:33.112 --> 00:53:36.300 You know we're just about out of time.
- NOTE Confidence: 0.83347088098526
- $00{:}53{:}36{.}300 \dashrightarrow 00{:}53{:}37{.}488$  An really appreciate.
- NOTE Confidence: 0.83347088098526
- 00:53:37.488 --> 00:53:39.072 Oh actually, JoJo contest
- NOTE Confidence: 0.83347088098526
- $00:53:39.072 \rightarrow 00:53:40.656$  hasn't question, forgive me.
- NOTE Confidence: 0.83347088098526
- 00:53:40.660 --> 00:53:42.988 So Joe's question is high dose
- NOTE Confidence: 0.83347088098526
- $00{:}53{:}42{.}988 \dashrightarrow 00{:}53{:}44{.}540$  radiation the rapy delivered to
- NOTE Confidence: 0.83347088098526
- $00{:}53{:}44.603 \dashrightarrow 00{:}53{:}47.015$  pediatric patients can lead to glioma?
- NOTE Confidence: 0.83347088098526
- $00{:}53{:}47{.}020 \dashrightarrow 00{:}53{:}49{.}714$  Have you found evidence that medical
- NOTE Confidence: 0.83347088098526
- $00:53:49.714 \rightarrow 00:53:51.988$  imaging and radiation exposure in
- NOTE Confidence: 0.83347088098526

 $00:53:51.988 \rightarrow 00:53:53.980$  this setting is associated? So

NOTE Confidence: 0.861393511295319

 $00:53:53.980 \rightarrow 00:53:55.805$  there's actually, and you probably

NOTE Confidence: 0.861393511295319

 $00:53:55.805 \dashrightarrow 00:53:58.210$  even know of these two studies.

NOTE Confidence: 0.861393511295319

 $00:53:58.210 \longrightarrow 00:54:00.583$  There's a big cohort from Australia as

NOTE Confidence: 0.861393511295319

 $00:54:00.583 \rightarrow 00:54:03.580$  well as a second cohort from England,

NOTE Confidence: 0.861393511295319

 $00:54:03.580 \longrightarrow 00:54:06.612$  and they did find that even exposure to NOTE Confidence: 0.861393511295319

 $00{:}54{:}06{.}612 \dashrightarrow 00{:}54{:}09{.}826$  head CT's at an early age in children

NOTE Confidence: 0.861393511295319

 $00:54:09.826 \dashrightarrow 00:54:12.029$  was associated with the I mean.

NOTE Confidence: 0.861393511295319

00:54:12.030 --> 00:54:14.718 It's a very small increase in risk,

NOTE Confidence: 0.861393511295319

 $00:54:14.720 \longrightarrow 00:54:16.760$  but a definite increase in risk

NOTE Confidence: 0.861393511295319

00:54:16.760 --> 00:54:18.940 of both glioma and meningioma,

NOTE Confidence: 0.861393511295319

 $00:54:18.940 \longrightarrow 00:54:21.076$  and then anything we looked at

NOTE Confidence: 0.861393511295319

 $00:54:21.076 \longrightarrow 00:54:24.237$  we did find it was a fairly hotly

NOTE Confidence: 0.861393511295319

 $00:54:24.237 \longrightarrow 00:54:26.302$  contested topic we did find.

NOTE Confidence: 0.861393511295319

 $00:54:26.310 \rightarrow 00:54:28.711$  And exposure to bite wings was associated

NOTE Confidence: 0.861393511295319

 $00:54:28.711 \rightarrow 00:54:30.908$  with an increased risk of meningioma,

- NOTE Confidence: 0.861393511295319
- $00:54:30.910 \longrightarrow 00:54:32.750$  but that's sort of exposure
- NOTE Confidence: 0.861393511295319
- $00:54:32.750 \rightarrow 00:54:34.810$  level in terms of dental X,
- NOTE Confidence: 0.861393511295319
- $00:54:34.810 \rightarrow 00:54:36.580$  Rays generally doesn't exist now.
- NOTE Confidence: 0.861393511295319
- 00:54:36.580 --> 00:54:39.044 But yeah, in terms of head CT's,
- NOTE Confidence: 0.861393511295319
- $00:54:39.050 \rightarrow 00:54:41.180$  the two big cohorts from Australia,
- NOTE Confidence: 0.861393511295319
- $00:54:41.180 \longrightarrow 00:54:42.950$  anyone to do suggest that,
- NOTE Confidence: 0.861393511295319
- 00:54:42.950 --> 00:54:44.009 although you know,
- NOTE Confidence: 0.861393511295319
- $00:54:44.009 \rightarrow 00:54:46.127$  even though the risk is increased,
- NOTE Confidence: 0.861393511295319
- $00{:}54{:}46{.}130 \dashrightarrow 00{:}54{:}47{.}198$  the absolute numbers
- NOTE Confidence: 0.815169589860099
- $00:54:47.200 \longrightarrow 00:54:49.110$  are small. And then Antonio
- NOTE Confidence: 0.815169589860099
- 00:54:49.110 --> 00:54:51.002 Murray asks, is great talk.
- NOTE Confidence: 0.815169589860099
- $00:54:51.002 \rightarrow 00:54:53.246$  Have you looked at thyroid hormones,
- NOTE Confidence: 0.815169589860099
- 00:54:53.250 00:54:54.750 thyroid disease and differences
- NOTE Confidence: 0.815169589860099
- $00:54:54.750 \longrightarrow 00:54:56.250$  between men and women?
- NOTE Confidence: 0.837125480175018
- $00:54:57.020 \longrightarrow 00:54:59.939$  So we haven't but one thing that
- NOTE Confidence: 0.837125480175018

00:54:59.939 - > 00:55:02.438 is very interesting, and it relates

NOTE Confidence: 0.837125480175018

00:55:02.438 --> 00:55:04.934 a little bit more to meningioma.

NOTE Confidence: 0.837125480175018

 $00:55:04.940 \longrightarrow 00:55:07.448$  Is a gene that we found,

NOTE Confidence: 0.837125480175018

 $00{:}55{:}07{.}450 \dashrightarrow 00{:}55{:}09{.}530$  and this is a constitutional

NOTE Confidence: 0.837125480175018

 $00:55:09.530 \longrightarrow 00:55:11.194$  gene on chromosome 10.

NOTE Confidence: 0.837125480175018

 $00{:}55{:}11.200 \dashrightarrow 00{:}55{:}14.119$  We've found to be associated with meningioma,

NOTE Confidence: 0.837125480175018

 $00:55:14.120 \longrightarrow 00:55:16.200$  breast, ovarian and also now

NOTE Confidence: 0.837125480175018

 $00:55:16.200 \longrightarrow 00:55:20.270$  thyroid tumors. Interest.

NOTE Confidence: 0.886166334152222

 $00:55:20.270 \longrightarrow 00:55:21.176$  Elizabeth, thank you.

NOTE Confidence: 0.886166334152222

 $00:55:21.176 \longrightarrow 00:55:23.690$  We are at the top of the hour.

NOTE Confidence: 0.886166334152222

 $00:55:23.690 \dashrightarrow 00:55:25.245$  Appreciate both your talk and

NOTE Confidence: 0.886166334152222

00:55:25.245 --> 00:55:26.489 Barbara's really extending work.

NOTE Confidence: 0.886166334152222

00:55:26.490 --> 00:55:28.770 Thank you for sharing all of it with

NOTE Confidence: 0.886166334152222

 $00:55:28.770 \rightarrow 00:55:31.470$  us and to everyone who joins us today.

NOTE Confidence: 0.886166334152222

00:55:31.470 - 00:55:33.528 Thank you for taking the time

NOTE Confidence: 0.886166334152222

 $00:55:33.528 \rightarrow 00:55:35.623$  to join grand rounds and we'll

NOTE Confidence: 0.886166334152222 00:55:35.623 --> 00:55:37.579 see you all again next week. NOTE Confidence: 0.886166334152222 00:55:37.580 --> 00:55:39.648 Have a good day.