WEBVTT

NOTE duration:"01:09:37"

NOTE recognizability:0.792

NOTE language:en-us

NOTE Confidence: 0.7803253066666667

 $00{:}00{:}00{.}000$  -->  $00{:}00{:}04.518$  Just a minute after noon, so I'd like to.

NOTE Confidence: 0.7803253066666667

 $00:00:04.520 \rightarrow 00:00:06.428$  A few people are still arriving,

NOTE Confidence: 0.7803253066666667

 $00:00:06.430 \rightarrow 00:00:10.083$  but I'd like to to welcome everybody today

NOTE Confidence: 0.7803253066666667

 $00:00:10.083 \rightarrow 00:00:12.834$  to the Cancer Center ground grand Rounds.

NOTE Confidence: 0.7803253066666667

00:00:12.840 --> 00:00:14.810 And for those of you who who don't know me,

NOTE Confidence: 0.7803253066666667

00:00:14.810 --> 00:00:16.181 I'm Mark Lemmon.

NOTE Confidence: 0.7803253066666667

 $00{:}00{:}16.181 \dashrightarrow 00{:}00{:}19.600$  I'm stepping in for Eric Weiner today

NOTE Confidence: 0.7803253066666667

 $00:00:19.600 \rightarrow 00:00:22.950$  because Eric is otherwise engaged.

NOTE Confidence: 0.7803253066666667

 $00:00:22.950 \longrightarrow 00:00:25.440$  I'm mark them and I'm deputy

NOTE Confidence: 0.7803253066666667

 $00{:}00{:}25{.}440 \dashrightarrow 00{:}00{:}28{.}429$  director of of the Cancer Centre.

NOTE Confidence: 0.7803253066666667

00:00:28.430 --> 00:00:33.042 And so I'm I'm I'm channeling.

NOTE Confidence: 0.7803253066666667

00:00:33.042 --> 00:00:36.210 Actually, which is why I won't do it so.

NOTE Confidence: 0.7803253066666667

 $00:00:36.210 \longrightarrow 00:00:37.137$  But the great,

 $00:00:37.137 \rightarrow 00:00:40.339$  great to have you all here and great to have.

NOTE Confidence: 0.7803253066666667

00:00:40.340 --> 00:00:43.874 Louise Escobar Hoyos and rose and

NOTE Confidence: 0.7803253066666667

 $00:00:43.874 \longrightarrow 00:00:47.803$  we know Zikula to talk with us

NOTE Confidence: 0.7803253066666667

 $00:00:47.803 \rightarrow 00:00:51.753$  today and we so we begin with with

NOTE Confidence: 0.7803253066666667

 $00:00:51.753 \dashrightarrow 00:00:54.518$  Doctor Louisa has Escobar holes.

NOTE Confidence: 0.7803253066666667

 $00:00:54.520 \longrightarrow 00:00:57.005$  Who is an assistant professor

NOTE Confidence: 0.7803253066666667

00:00:57.005 --> 00:00:58.496 of the rapeutic radiology.

NOTE Confidence: 0.7803253066666667

 $00:00:58.500 \rightarrow 00:01:00.642$  She received her Masters degree in

NOTE Confidence: 0.7803253066666667

 $00{:}01{:}00{.}642 \dashrightarrow 00{:}01{:}02{.}462$  Biomedical Sciences at the University

NOTE Confidence: 0.7803253066666667

 $00:01:02.462 \longrightarrow 00:01:04.765$  at Del Valley in Cali in Colombia.

NOTE Confidence: 0.7803253066666667

 $00{:}01{:}04.770 \dashrightarrow 00{:}01{:}06.438$  And then as a Fulbright Scholarship,

NOTE Confidence: 0.7803253066666667

 $00:01:06.440 \longrightarrow 00:01:08.690$  pursued a cache in in cancer,

NOTE Confidence: 0.7803253066666667

00:01:08.690 --> 00:01:10.038 molecular and cellular pharmacology

NOTE Confidence: 0.7803253066666667

00:01:10.038 --> 00:01:11.386 at Stony Brook University,

NOTE Confidence: 0.7803253066666667

 $00:01:11.390 \longrightarrow 00:01:13.390$  where she was mentored by

NOTE Confidence: 0.7803253066666667

00:01:13.390 --> 00:01:14.590 Doctor Kenneth Schroyer,

- NOTE Confidence: 0.7803253066666667
- $00:01:14.590 \rightarrow 00:01:16.225$  then completed her postdoctoral training
- NOTE Confidence: 0.7803253066666667
- 00:01:16.225 --> 00:01:18.210 at Memorial Sloan Kettering Cancer Center.
- NOTE Confidence: 0.7803253066666667
- $00:01:18.210 \longrightarrow 00:01:20.800$  Commented by Doctor Stephen Stephen
- NOTE Confidence: 0.7803253066666667
- 00:01:20.800 --> 00:01:23.390 Leach and Omar Abdel Wahab,
- NOTE Confidence: 0.7803253066666667
- $00:01:23.390 \rightarrow 00:01:26.946$  and the overarching goal of Doctor Escobar.
- NOTE Confidence: 0.7803253066666667
- 00:01:26.950 --> 00:01:29.710 Hoyos's lab is to develop new
- NOTE Confidence: 0.7803253066666667
- $00:01:29.710 \longrightarrow 00:01:31.589$  approaches to tackling pancreatic
- NOTE Confidence: 0.7803253066666667
- $00:01:31.589 \longrightarrow 00:01:34.427$  and lung cancers with lots of.
- NOTE Confidence: 0.7803253066666667
- 00:01:34.430 --> 00:01:36.006 Really very exciting work.
- NOTE Confidence: 0.7803253066666667
- 00:01:36.006 --> 00:01:38.888 Exciting new work going on and lots
- NOTE Confidence: 0.7803253066666667
- 00:01:38.888 --> 00:01:41.103 of innovation and specifically her
- NOTE Confidence: 0.7803253066666667
- 00:01:41.103 --> 00:01:43.898 team is currently trying to seeking
- NOTE Confidence: 0.7803253066666667
- $00{:}01{:}43.898 \dashrightarrow 00{:}01{:}46.283$  to understand and target somatic
- NOTE Confidence: 0.7803253066666667
- $00{:}01{:}46.283 \dashrightarrow 00{:}01{:}48.089$  mutations and importantly aberrant
- NOTE Confidence: 0.7803253066666667
- $00:01:48.089 \dashrightarrow 00:01:50.303$  RNA processing in these tumors in
- NOTE Confidence: 0.7803253066666667

 $00:01:50.303 \rightarrow 00:01:53.130$  order to to develop novel therapies.

NOTE Confidence: 0.7803253066666667

 $00{:}01{:}53.130 \dashrightarrow 00{:}01{:}55.398$  So it's a great pleasure to have

NOTE Confidence: 0.7803253066666667

 $00:01:55.398 \longrightarrow 00:01:56.730$  you start us off.

NOTE Confidence: 0.7803253066666667

00:01:56.730 --> 00:01:58.508 Louisa and I look forward very much

NOTE Confidence: 0.7803253066666667

 $00:01:58.508 \longrightarrow 00:02:01.020$  to your talk, so please take it away.

NOTE Confidence: 0.882051635384615

 $00:02:02.630 \dashrightarrow 00:02:05.892$  Wonderful thank you Mark. Let me just NOTE Confidence: 0.882051635384615

 $00:02:05.892 \rightarrow 00:02:08.928$  can everyone see my presenter mode.

NOTE Confidence: 0.882051635384615

 $00{:}02{:}08{.}930 \dashrightarrow 00{:}02{:}10{.}995$  Sorry not my presenter. My full slide

NOTE Confidence: 0.592765046166667

 $00{:}02{:}11.670 \dashrightarrow 00{:}02{:}14.120$  slide that's all very good perfect. So

NOTE Confidence: 0.885106782105263

00:02:14.130 --> 00:02:16.447 thank you Mark again for that Nice

NOTE Confidence: 0.885106782105263

 $00{:}02{:}16{.}447 \dashrightarrow 00{:}02{:}18{.}189$  introduction and thank you every one

NOTE Confidence: 0.885106782105263

 $00{:}02{:}18.189 \dashrightarrow 00{:}02{:}20.241$  for participating today in in the

NOTE Confidence: 0.885106782105263

00:02:20.241 --> 00:02:21.950 Cancer Center grand rounds and I'm

NOTE Confidence: 0.885106782105263

 $00{:}02{:}21{.}950 \dashrightarrow 00{:}02{:}24{.}136$  excited to share with you a little bit

NOTE Confidence: 0.885106782105263

 $00:02:24.136 \rightarrow 00:02:25.935$  of the research that we've been doing

NOTE Confidence: 0.885106782105263

00:02:25.986 --> 00:02:27.874 in our lab in terms of finding how

- NOTE Confidence: 0.885106782105263
- $00:02:27.874 \rightarrow 00:02:30.540$  altered our release by splicing is a
- NOTE Confidence: 0.885106782105263
- $00:02:30.540 \longrightarrow 00:02:32.730$  driver event for pancreatic cancer.
- NOTE Confidence: 0.885106782105263
- $00{:}02{:}32{.}730 \dashrightarrow 00{:}02{:}35{.}906$  So if your disclosures I'm part of the
- NOTE Confidence: 0.885106782105263
- 00:02:35.906 --> 00:02:38.488 Scientific Advisory Board of QDX Diagnostics,
- NOTE Confidence: 0.885106782105263
- $00:02:38.490 \longrightarrow 00:02:40.062$  I won't be presenting the work
- NOTE Confidence: 0.885106782105263
- $00{:}02{:}40.062 \dashrightarrow 00{:}02{:}41.789$  that I have with them today.
- NOTE Confidence: 0.885106782105263
- $00:02:41.790 \longrightarrow 00:02:43.326$  I'll be talking about this compound.
- NOTE Confidence: 0.885106782105263
- $00:02:43.330 \longrightarrow 00:02:45.195$  This small molecule inhibitor of
- NOTE Confidence: 0.885106782105263
- $00{:}02{:}45{.}195 \dashrightarrow 00{:}02{:}47{.}403$  splicing that has been provided to
- NOTE Confidence: 0.885106782105263
- $00:02:47.403 \rightarrow 00:02:49.398$  us by age 3 biomedicine and currently
- NOTE Confidence: 0.885106782105263
- $00:02:49.398 \longrightarrow 00:02:51.560$  we're in discussions to launch a
- NOTE Confidence: 0.885106782105263
- $00:02:51.560 \rightarrow 00:02:53.470$  clinical trial using this compound.
- NOTE Confidence: 0.885106782105263
- $00{:}02{:}53.470 \dashrightarrow 00{:}02{:}54.970$  Based on the research that I'm
- NOTE Confidence: 0.885106782105263
- $00:02:54.970 \longrightarrow 00:02:56.340$  going to show you today.
- NOTE Confidence: 0.885106782105263
- $00:02:56.340 \longrightarrow 00:02:59.080$  So for many of you,
- NOTE Confidence: 0.885106782105263

 $00:02:59.080 \rightarrow 00:03:01.450$  it's not unheard of that pancreatic

NOTE Confidence: 0.885106782105263

 $00{:}03{:}01{.}450 \dashrightarrow 00{:}03{:}04{.}479$  cancer is a very lethal malignancy,

NOTE Confidence: 0.885106782105263

 $00:03:04.480 \longrightarrow 00:03:07.420$  and in here is just plotting

NOTE Confidence: 0.885106782105263

 $00:03:07.420 \longrightarrow 00:03:09.380$  the survival over time.

NOTE Confidence: 0.885106782105263

 $00{:}03{:}09{.}380 \dashrightarrow 00{:}03{:}10{.}969$  For the major cancers and what we

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 $00{:}03{:}10{.}969 \dashrightarrow 00{:}03{:}12{.}931$  can see in this evidence is that

NOTE Confidence: 0.885106782105263

 $00{:}03{:}12{.}931 \dashrightarrow 00{:}03{:}14{.}761$  unfortunately we haven't been able to

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 $00{:}03{:}14.818 \dashrightarrow 00{:}03{:}16.883$  make that much improvement in the five

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00:03:16.883 --> 00:03:18.781 year survival rate of pancreatic cancer,

NOTE Confidence: 0.885106782105263

 $00:03:18.781 \rightarrow 00:03:21.478$  and this could be attributed to many reasons.

NOTE Confidence: 0.885106782105263

 $00:03:21.478 \longrightarrow 00:03:23.764$  It's it's a. It's a disease that

NOTE Confidence: 0.885106782105263

 $00:03:23.764 \longrightarrow 00:03:25.690$  is diagnosed once it has been.

NOTE Confidence: 0.885106782105263

 $00:03:25.690 \longrightarrow 00:03:26.710$  It's already systemic.

NOTE Confidence: 0.885106782105263

 $00:03:26.710 \longrightarrow 00:03:27.730$  The first line,

NOTE Confidence: 0.885106782105263

 $00:03:27.730 \rightarrow 00:03:29.842$  chemotherapy and immunotherapies,

NOTE Confidence: 0.885106782105263

 $00:03:29.842 \rightarrow 00:03:31.250$  are ineffective,

 $00:03:31.250 \rightarrow 00:03:33.185$  and the available targeted therapies

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 $00:03:33.185 \longrightarrow 00:03:35.385$  are only available to 1% of

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00:03:35.385 - 00:03:36.710 the cases that have actionable,

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 $00:03:36.710 \longrightarrow 00:03:37.564$  actionable mutations.

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 $00:03:37.564 \rightarrow 00:03:39.699$  So there is a really.

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 $00:03:39.700 \rightarrow 00:03:42.108$  Strong clinical need to understand more of

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 $00:03:42.108 \rightarrow 00:03:44.540$  these tumors and develop new treatments.

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 $00:03:44.540 \longrightarrow 00:03:46.367$  So just to introduce a little bit

NOTE Confidence: 0.885106782105263

 $00:03:46.367 \longrightarrow 00:03:47.849$  of the mutational landscape for

NOTE Confidence: 0.885106782105263

 $00:03:47.849 \longrightarrow 00:03:49.459$  these tumors and mainly today,

NOTE Confidence: 0.885106782105263

00:03:49.460 --> 00:03:50.936 I'm talking about pancreatic

NOTE Confidence: 0.885106782105263

 $00:03:50.936 \longrightarrow 00:03:53.150$  ductal at no carcinomas or petax,

NOTE Confidence: 0.885106782105263

 $00:03:53.150 \rightarrow 00:03:55.684$  the most common form of pancreatic cancer,

NOTE Confidence: 0.885106782105263

 $00:03:55.690 \rightarrow 00:03:57.922$  so we know that there are driven by a

NOTE Confidence: 0.885106782105263

 $00{:}03{:}57{.}922 \dashrightarrow 00{:}03{:}59{.}944$  first mutation, first hit mutation,

 $00:03:59.944 \rightarrow 00:04:01.536$  activating mutations in cameras,

NOTE Confidence: 0.885106782105263

 $00{:}04{:}01{.}540 \dashrightarrow 00{:}04{:}04{.}109$  and also is very common to find

NOTE Confidence: 0.885106782105263

00:04:04.110 --> 00:04:04.638 T53 mutations,

NOTE Confidence: 0.885106782105263

 $00:04:04.638 \longrightarrow 00:04:06.222$  so we'll talk about a little

NOTE Confidence: 0.885106782105263

 $00:04:06.222 \longrightarrow 00:04:07.770$  bit more of these mutations.

NOTE Confidence: 0.885106782105263

 $00{:}04{:}07{.}770 \dashrightarrow 00{:}04{:}10{.}227$  There is also sometimes it appears that

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 $00:04:10.227 \rightarrow 00:04:12.009$  other tumor suppressors are mutated,

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 $00:04:12.010 \dashrightarrow 00:04:14.516$  and then after these four top genes.

NOTE Confidence: 0.885106782105263

00:04:14.520 --> 00:04:16.386 There's really a sea of mutations

NOTE Confidence: 0.885106782105263

 $00:04:16.386 \rightarrow 00:04:18.879$  that appear at a very low frequency,

NOTE Confidence: 0.885106782105263

 $00:04:18.880 \longrightarrow 00:04:22.000$  so using mouse models over the

NOTE Confidence: 0.885106782105263

 $00:04:22.000 \longrightarrow 00:04:24.095$  last 1520 years or so we have been

NOTE Confidence: 0.885106782105263

 $00{:}04{:}24.095 \dashrightarrow 00{:}04{:}25.963$  able to kind of dissect a little

NOTE Confidence: 0.885106782105263

 $00:04:25.963 \longrightarrow 00:04:27.667$  bit the genetics of this disease.

NOTE Confidence: 0.885106782105263

 $00:04:27.670 \rightarrow 00:04:29.836$  We know that the normal pancreas,

NOTE Confidence: 0.885106782105263

00:04:29.840 - > 00:04:31.484 if we engineer key rest mutations

- NOTE Confidence: 0.885106782105263
- $00:04:31.484 \rightarrow 00:04:33.200$  into the US and ourselves,
- NOTE Confidence: 0.885106782105263
- $00:04:33.200 \longrightarrow 00:04:35.040$  these mice will start develop,
- NOTE Confidence: 0.885106782105263
- 00:04:35.040 --> 00:04:37.568 panning or pancreatic intraepithelial
- NOTE Confidence: 0.885106782105263
- $00{:}04{:}37{.}568 \dashrightarrow 00{:}04{:}40{.}573$  lesions that will progress into
- NOTE Confidence: 0.885106782105263
- 00:04:40.573 --> 00:04:42.938 pancreatic cancer if we add
- NOTE Confidence: 0.885106782105263
- $00:04:42.938 \longrightarrow 00:04:45.240$  an additional mutation in P50.
- NOTE Confidence: 0.885106782105263
- 00:04:45.240 --> 00:04:46.488 And so basically,
- NOTE Confidence: 0.885106782105263
- $00{:}04{:}46{.}488 \dashrightarrow 00{:}04{:}49{.}877$  this is this tumor follows kind of a
- NOTE Confidence: 0.885106782105263
- $00{:}04{:}49.877 \dashrightarrow 00{:}04{:}52.229$  two hit hypothesis notes and model
- NOTE Confidence: 0.885106782105263
- $00:04:52.229 \longrightarrow 00:04:55.378$  and all with the with you know to
- NOTE Confidence: 0.885106782105263
- $00:04:55.378 \rightarrow 00:04:58.790$  enhance the activity of kieras over the time.
- NOTE Confidence: 0.885106782105263
- 00:04:58.790 --> 00:05:00.575 Now for many years we've known about
- NOTE Confidence: 0.885106782105263
- $00:05:00.575 \rightarrow 00:05:02.349$  these two mutations driving this disease,
- NOTE Confidence: 0.885106782105263
- $00{:}05{:}02{.}350 \dashrightarrow 00{:}05{:}04{.}744$  but really we haven't made much effort
- NOTE Confidence: 0.885106782105263
- $00{:}05{:}04.744 \dashrightarrow 00{:}05{:}06.672$  to understand how these oncoproteins
- NOTE Confidence: 0.885106782105263

 $00:05:06.672 \rightarrow 00:05:09.612$  cooperate in the case of pancreatic cancer,

NOTE Confidence: 0.885106782105263

 $00:05:09.620 \longrightarrow 00:05:10.844$  and even other tumors.

NOTE Confidence: 0.885106782105263

 $00:05:10.844 \rightarrow 00:05:12.680$  So a few years ago when

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00:05:12.750 --> 00:05:15.279 I was gonna start as a postdoc at MSK,

NOTE Confidence: 0.827377530526316

 $00{:}05{:}15.280 \dashrightarrow 00{:}05{:}18.458$  these studies came out in the molecular

NOTE Confidence: 0.827377530526316

00:05:18.458 --> 00:05:21.148 subtypes of pancreatic cancer with the NOTE Confidence: 0.827377530526316

 $00:05:21.148 \longrightarrow 00:05:23.650$  squamous and basal subtype being the

NOTE Confidence: 0.827377530526316

 $00:05:23.650 \rightarrow 00:05:25.538$  most aggressive molecular subtypes.

NOTE Confidence: 0.827377530526316

 $00{:}05{:}25{.}538 \dashrightarrow 00{:}05{:}28{.}170$  And when you look into what genes are

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 $00:05:28.232 \dashrightarrow 00:05:30.657$  differentially expressed into the subtype,

NOTE Confidence: 0.827377530526316

 $00{:}05{:}30{.}660 \dashrightarrow 00{:}05{:}33{.}909$  there is a small subset of genes that it's

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 $00:05:33.909 \dashrightarrow 00:05:36.017$  over expressed in this molecular subtype.

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 $00:05:36.020 \rightarrow 00:05:38.044$  And when you look into their mutation status,

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 $00:05:38.050 \rightarrow 00:05:39.402$  they're highly associated with

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00:05:39.402 --> 00:05:41.476 gain of function mutant, P. 53.

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 $00:05:41.476 \longrightarrow 00:05:43.624$  And these genes that are being

 $00:05:43.624 \rightarrow 00:05:46.490$  enriched are the majority are codeine

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00:05:46.490 --> 00:05:48.566 for splicing regulatory proteins.

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 $00{:}05{:}48.570 \dashrightarrow 00{:}05{:}50.594$  So after I read these reports I kind

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 $00:05:50.594 \rightarrow 00:05:52.400$  of got interested on understanding

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 $00{:}05{:}52{.}400 \dashrightarrow 00{:}05{:}54{.}872$  a little bit more alternative RNA

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 $00{:}05{:}54.872 \dashrightarrow 00{:}05{:}57.409$  splicing and just to remind every one

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 $00:05:57.409 \rightarrow 00:05:58.645$  during alternative splicing.

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 $00:05:58.650 \rightarrow 00:06:01.258$  Not only we remove the introns of genes

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 $00{:}06{:}01.258 \dashrightarrow 00{:}06{:}03.747$  but also there could be a selective

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 $00{:}06{:}03.750 \dashrightarrow 00{:}06{:}06.172$  retention or skipping of exons and this

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 $00:06:06.172 \longrightarrow 00:06:09.018$  can lead to protein that had opposite

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 $00:06:09.018 \rightarrow 00:06:11.622$  functions or no protein being formed.

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00:06:11.630 -> 00:06:13.415 And we all have our favorite gene,

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 $00{:}06{:}13.420 \dashrightarrow 00{:}06{:}15.586$  and sometimes we don't study the

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 $00:06:15.586 \dashrightarrow 00:06:17.377$  alternative splicing of these gene

 $00:06:17.377 \longrightarrow 00:06:19.372$  and this pathway in general is a

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 $00{:}06{:}19{.}372 \dashrightarrow 00{:}06{:}21{.}170$  very potent and plastic that can

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 $00:06:21.170 \longrightarrow 00:06:23.340$  actually explain a lot of the features

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 $00:06:23.340 \longrightarrow 00:06:25.440$  that happen in cancer cells.

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 $00{:}06{:}25{.}440 \dashrightarrow 00{:}06{:}28{.}694$  So based on those reports I

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 $00{:}06{:}28.694 \dashrightarrow 00{:}06{:}29.576$  asked the question,

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 $00{:}06{:}29{.}576 \dashrightarrow 00{:}06{:}31{.}340$  is there a connection between mutations

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 $00{:}06{:}31.395 \dashrightarrow 00{:}06{:}33.466$  and P53 and alterations in RNA splicing

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 $00{:}06{:}33.466 \dashrightarrow 00{:}06{:}36.245$  and so first we took the RNA sequencing

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 $00:06:36.245 \dashrightarrow 00:06:38.393$  from many patients and we divided

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 $00:06:38.463 \dashrightarrow 00:06:40.538$  them into three different groups,

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 $00{:}06{:}40{.}540 \dashrightarrow 00{:}06{:}42{.}180$  either if they had truncating.

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 $00:06:42.180 \longrightarrow 00:06:44.450$  Mutations in P53 meaning loss

NOTE Confidence: 0.827377530526316

00:06:44.450 --> 00:06:46.653 of function mutations of P53,

NOTE Confidence: 0.827377530526316

 $00:06:46.653 \longrightarrow 00:06:48.568$  gain of function mutations or

NOTE Confidence: 0.827377530526316

 $00{:}06{:}48.568 \dashrightarrow 00{:}06{:}50.543$  mutations that make the protein

- NOTE Confidence: 0.827377530526316
- $00:06:50.543 \rightarrow 00:06:52.799$  going from a tumor suppressor to

00:06:52.799 --> 00:06:55.151 an uncle protein or wild type P53.

NOTE Confidence: 0.827377530526316

 $00{:}06{:}55{.}151 \dashrightarrow 00{:}06{:}56{.}956$  And we compared this glycine.

NOTE Confidence: 0.827377530526316

 $00:06:56.960 \dashrightarrow 00:06:58.840$  Differences between these tumors and

NOTE Confidence: 0.827377530526316

 $00:06:58.840 \longrightarrow 00:07:01.210$  in the case of pancreatic cancer,

NOTE Confidence: 0.827377530526316

 $00:07:01.210 \dashrightarrow 00:07:03.610$  the most common hotspot missense

NOTE Confidence: 0.827377530526316

 $00:07:03.610 \longrightarrow 00:07:06.470$  mutations are these four listed here.

NOTE Confidence: 0.827377530526316

 $00:07:06.470 \longrightarrow 00:07:08.210$  So here are the 1st results.

NOTE Confidence: 0.827377530526316

 $00:07:08.210 \longrightarrow 00:07:10.706$  So in in the X axis you have

NOTE Confidence: 0.827377530526316

 $00{:}07{:}10.706 \dashrightarrow 00{:}07{:}12.519$  a measurement of alternative.

NOTE Confidence: 0.827377530526316

 $00:07:12.520 \rightarrow 00:07:15.229$  Slicing of axons and the different tumors,

NOTE Confidence: 0.827377530526316

 $00{:}07{:}15.230 \dashrightarrow 00{:}07{:}17.606$  and here is each one of the mutations.

NOTE Confidence: 0.827377530526316

 $00:07:17.610 \longrightarrow 00:07:20.410$  53 compared to the wild type P53 tumors,

NOTE Confidence: 0.827377530526316

 $00{:}07{:}20{.}410 \dashrightarrow 00{:}07{:}22{.}930$  and each one of the hotspot mutations

NOTE Confidence: 0.827377530526316

 $00{:}07{:}22.930 \dashrightarrow 00{:}07{:}25.166$  compared to truncated P53 and what you

 $00:07:25.166 \rightarrow 00:07:27.404$  are can appreciate is that all these

NOTE Confidence: 0.827377530526316

00:07:27.404 --> 00:07:29.614 hot<br/>spot gain of function mutations

NOTE Confidence: 0.827377530526316

00:07:29.614 --> 00:07:31.698 change alternative splicing and the

NOTE Confidence: 0.827377530526316

00:07:31.698 --> 00:07:33.230 R175 one of the most common ones,

NOTE Confidence: 0.827377530526316

 $00:07:33.230 \longrightarrow 00:07:34.594$  actually changes the most.

NOTE Confidence: 0.827377530526316

 $00{:}07{:}34.594 \dashrightarrow 00{:}07{:}36.299$  So based on those correlation

NOTE Confidence: 0.827377530526316

 $00{:}07{:}36.299 \dashrightarrow 00{:}07{:}37.930$  studies we started asking well.

NOTE Confidence: 0.827377530526316

 $00:07:37.930 \longrightarrow 00:07:40.090$  Is P53 changing splicing

NOTE Confidence: 0.827377530526316

 $00{:}07{:}40{.}090 \dashrightarrow 00{:}07{:}41{.}710$  and pancreatic cancer?

NOTE Confidence: 0.827377530526316

 $00:07:41.710 \longrightarrow 00:07:43.360$  So we went ahead and developed.

NOTE Confidence: 0.827377530526316

 $00{:}07{:}43.360 \dashrightarrow 00{:}07{:}45.240$  Three different model system patient

NOTE Confidence: 0.827377530526316

 $00{:}07{:}45.240 \dashrightarrow 00{:}07{:}47.120$  derived organoids where we can

NOTE Confidence: 0.827377530526316

 $00{:}07{:}47.184 \dashrightarrow 00{:}07{:}48.900$  actually shut off the expression of

NOTE Confidence: 0.827377530526316

00:07:48.900 --> 00:07:51.556 the mutant P 53 and after doing deep

NOTE Confidence: 0.827377530526316

 $00{:}07{:}51{.}556$  -->  $00{:}07{:}53{.}366$  RNA sequencing and splicing analysis,

NOTE Confidence: 0.827377530526316

 $00{:}07{:}53.370 \dashrightarrow 00{:}07{:}56.282$  we can see that there are these different

 $00:07:56.282 \rightarrow 00:07:58.218$  exons that are either preferentially

NOTE Confidence: 0.827377530526316

00:07:58.218 --> 00:08:00.513 retained in red or preferentially

NOTE Confidence: 0.827377530526316

 $00:08:00.513 \longrightarrow 00:08:03.337$  spliced out in the context of mutant

NOTE Confidence: 0.827377530526316

 $00:08:03.340 \longrightarrow 00:08:05.728$  P53 in complex to complement this

NOTE Confidence: 0.827377530526316

 $00:08:05.728 \rightarrow 00:08:08.650$  model we generated a murine cell line,

NOTE Confidence: 0.827377530526316

 $00{:}08{:}08{.}650 \dashrightarrow 00{:}08{:}10.895$  also with the same capacity

NOTE Confidence: 0.827377530526316

 $00:08:10.895 \longrightarrow 00:08:13.510$  to shut down mutant P 53.

NOTE Confidence: 0.827377530526316

 $00:08:13.510 \longrightarrow 00:08:14.142$  And again,

NOTE Confidence: 0.827377530526316

 $00:08:14.142 \longrightarrow 00:08:15.722$  we were seeing these changes

NOTE Confidence: 0.827377530526316

 $00:08:15.722 \rightarrow 00:08:17.080$  or swapping of axons.

NOTE Confidence: 0.698071543428571

 $00:08:17.080 \longrightarrow 00:08:20.380$  And lastly, we took a

NOTE Confidence: 0.698071543428571

 $00:08:20.380 \dashrightarrow 00:08:22.172$  pancreatic precancer mouse,

NOTE Confidence: 0.698071543428571

 $00{:}08{:}22.172 \dashrightarrow 00{:}08{:}24.532$  panning organoids where we knocking

NOTE Confidence: 0.698071543428571

 $00{:}08{:}24.532 \dashrightarrow 00{:}08{:}27.536$  the mutation of our 175 and again we

NOTE Confidence: 0.698071543428571

 $00{:}08{:}27.536 \dashrightarrow 00{:}08{:}29.581$  were seeing that even in early stages

 $00:08:29.581 \longrightarrow 00:08:32.053$  after early 19 of the mutation we were

NOTE Confidence: 0.698071543428571

 $00:08:32.053 \rightarrow 00:08:34.556$  seeing this differential splicing of exons,

NOTE Confidence: 0.698071543428571

 $00:08:34.560 \longrightarrow 00:08:35.630$  so we wanted to ask,

NOTE Confidence: 0.698071543428571

 $00:08:35.630 \longrightarrow 00:08:37.520$  what are the specific features

NOTE Confidence: 0.698071543428571

 $00{:}08{:}37{.}520 \dashrightarrow 00{:}08{:}39{.}608$  of these exons that are being

NOTE Confidence: 0.698071543428571

 $00:08:39.608 \rightarrow 00:08:40.936$  either retained or skipped?

NOTE Confidence: 0.698071543428571

 $00{:}08{:}40{.}940 \dashrightarrow 00{:}08{:}43{.}622$  And we found that there is this that.

NOTE Confidence: 0.698071543428571

 $00:08:43.630 \rightarrow 00:08:46.766$  The retention of these axles is not random.

NOTE Confidence: 0.698071543428571

 $00{:}08{:}46.770 \dashrightarrow 00{:}08{:}48.714$  All the promoted axons after splicing

NOTE Confidence: 0.698071543428571

 $00:08:48.714 \longrightarrow 00:08:50.824$  those ones that are going to be

NOTE Confidence: 0.698071543428571

 $00:08:50.824 \rightarrow 00:08:53.036$  retained in the mature M RNA are highly

NOTE Confidence: 0.698071543428571

 $00:08:53.036 \rightarrow 00:08:55.424$  enriched for seas while they're repressed,

NOTE Confidence: 0.698071543428571

00:08:55.430 --> 00:08:57.950 exiles were highly enriched in a S&G's,

NOTE Confidence: 0.698071543428571

 $00:08:57.950 \rightarrow 00:09:00.656$  suggesting that this was pretty much

NOTE Confidence: 0.698071543428571

 $00:09:00.656 \rightarrow 00:09:03.429$  a program established in these cells,

NOTE Confidence: 0.698071543428571

 $00:09:03.430 \longrightarrow 00:09:05.854$  so we wanted to focus on what were

 $00:09:05.854 \rightarrow 00:09:08.302$  the MRE's that were being coded by

NOTE Confidence: 0.698071543428571

 $00{:}09{:}08{.}302 \dashrightarrow 00{:}09{:}11{.}333$  these gain of of policy axons and so

NOTE Confidence: 0.698071543428571

 $00{:}09{:}11.333 \dashrightarrow 00{:}09{:}14.150$  here we're summing into one of these.

NOTE Confidence: 0.698071543428571

 $00:09:14.150 \longrightarrow 00:09:15.578$  Barneys Gap 17.

NOTE Confidence: 0.698071543428571

 $00{:}09{:}15{.}578 \dashrightarrow 00{:}09{:}17{.}958$  We're in mice and human.

NOTE Confidence: 0.698071543428571

00:09:17.960 --> 00:09:19.010 This Exxon 17,

NOTE Confidence: 0.698071543428571

 $00:09:19.010 \longrightarrow 00:09:20.760$  which is a policy Axon,

NOTE Confidence: 0.698071543428571

 $00:09:20.760 \longrightarrow 00:09:22.563$  is alternatively spliced,

NOTE Confidence: 0.698071543428571

 $00{:}09{:}22.563 \dashrightarrow 00{:}09{:}26.770$  and here are the raw sequencing of

NOTE Confidence: 0.698071543428571

 $00{:}09{:}26.879 \dashrightarrow 00{:}09{:}28.678$  the of the reeds of this Axon and

NOTE Confidence: 0.698071543428571

 $00{:}09{:}28.678 \dashrightarrow 00{:}09{:}30.214$  what you can appreciate is that

NOTE Confidence: 0.698071543428571

 $00:09:30.214 \dashrightarrow 00:09:32.174$  whenever the mutant P 53 is present,

NOTE Confidence: 0.698071543428571

 $00{:}09{:}32.180 \dashrightarrow 00{:}09{:}33.815$  there is higher rates versus

NOTE Confidence: 0.698071543428571

 $00{:}09{:}33{.}815 \dashrightarrow 00{:}09{:}35{.}450$  when you knock it down.

NOTE Confidence: 0.698071543428571

 $00:09:35.450 \longrightarrow 00:09:37.124$  There is a decrease on the

 $00:09:37.124 \rightarrow 00:09:38.240$  retention of these Axon,

NOTE Confidence: 0.698071543428571

 $00{:}09{:}38{.}240 \dashrightarrow 00{:}09{:}40{.}120$  but not the neighboring axons,

NOTE Confidence: 0.698071543428571

 $00:09:40.120 \longrightarrow 00:09:41.674$  and we saw this pattern across

NOTE Confidence: 0.698071543428571

 $00:09:41.674 \longrightarrow 00:09:43.644$  the marine cell line that we had

NOTE Confidence: 0.698071543428571

 $00:09:43.644 \rightarrow 00:09:45.104$  engineer in the panning organized.

NOTE Confidence: 0.698071543428571

 $00:09:45.110 \longrightarrow 00:09:47.590$  That we had also crisped.

NOTE Confidence: 0.698071543428571

 $00:09:47.590 \rightarrow 00:09:50.310$  So from here we actually went and said,

NOTE Confidence: 0.698071543428571

 $00:09:50.310 \longrightarrow 00:09:50.644$  well,

NOTE Confidence: 0.698071543428571

 $00:09:50.644 \dashrightarrow 00:09:52.648$  let's go back to patient derived

NOTE Confidence: 0.698071543428571

 $00:09:52.648 \rightarrow 00:09:55.001$  samples and let's see if the retention

NOTE Confidence: 0.698071543428571

 $00{:}09{:}55{.}001 \dashrightarrow 00{:}09{:}57{.}271$  of these policy accounting gap 17 is

NOTE Confidence: 0.698071543428571

00:09:57.271 --> 00:09:58.896 it exclusive for the R175 mutation,

NOTE Confidence: 0.698071543428571

 $00:09:58.896 \longrightarrow 00:10:00.737$  or is it also found in other

NOTE Confidence: 0.698071543428571

00:10:00.737 --> 00:10:02.640 gain of function mutants of P53?

NOTE Confidence: 0.698071543428571

 $00:10:02.640 \rightarrow 00:10:04.490$  And the answer was yes,

NOTE Confidence: 0.698071543428571

 $00:10:04.490 \rightarrow 00:10:07.392$  it's actually retained and not only are 175,

 $00:10:07.392 \dashrightarrow 00:10:09.862$  but other gain of function mutant P53.

NOTE Confidence: 0.698071543428571

00:10:09.862 $\operatorname{-->}$ 00:10:12.746 As you can appreciate here from this

NOTE Confidence: 0.698071543428571

 $00{:}10{:}12.746$  -->  $00{:}10{:}15.120$  targeted PCR. So then the question what?

NOTE Confidence: 0.698071543428571

 $00{:}10{:}15{.}120 \dashrightarrow 00{:}10{:}16{.}476$  It was well,

NOTE Confidence: 0.698071543428571

 $00:10:16.476 \rightarrow 00:10:19.188$  what is the consequence of incorporating

NOTE Confidence: 0.698071543428571

00:10:19.188 --> 00:10:21.899 policy exons into M RNA's over time,

NOTE Confidence: 0.698071543428571

 $00:10:21.900 \rightarrow 00:10:23.820$  and so when we started looking at all

NOTE Confidence: 0.698071543428571

 $00{:}10{:}23.820 \dashrightarrow 00{:}10{:}26.004$  of the M RNA's that were incorporating

NOTE Confidence: 0.698071543428571

 $00:10:26.004 \rightarrow 00:10:28.360$  policy axons in the presence of mutant P.

NOTE Confidence: 0.698071543428571

 $00:10:28.360 \longrightarrow 00:10:28.744 53,$ 

NOTE Confidence: 0.698071543428571

 $00:10:28.744 \longrightarrow 00:10:31.432$  we found that a family of proteins

NOTE Confidence: 0.698071543428571

 $00:10:31.432 \rightarrow 00:10:32.600$  called the GPA,

NOTE Confidence: 0.698071543428571

 $00{:}10{:}32.600 \dashrightarrow 00{:}10{:}35.528$  the GPA's activating proteins or gaps

NOTE Confidence: 0.698071543428571

 $00{:}10{:}35{.}528 \dashrightarrow 00{:}10{:}38{.}460$  were actually gaining these policy Axon.

NOTE Confidence: 0.698071543428571

 $00:10:38.460 \longrightarrow 00:10:41.004$  In fact 25% of total gaps encoded by

 $00:10:41.004 \rightarrow 00:10:43.395$  the human genome were gaining policy

NOTE Confidence: 0.698071543428571

 $00:10:43.395 \rightarrow 00:10:45.921$  exons and just to remind everyone.

NOTE Confidence: 0.698071543428571

 $00{:}10{:}45{.}930 \dashrightarrow 00{:}10{:}47{.}184$  The gaps do.

NOTE Confidence: 0.698071543428571

 $00:10:47.184 \rightarrow 00:10:49.274$  They actually accelerate the GTP

NOTE Confidence: 0.698071543428571

 $00{:}10{:}49{.}274 \dashrightarrow 00{:}10{:}51{.}206$  hydrolysis of Ras proteins so

NOTE Confidence: 0.698071543428571

 $00:10:51.206 \rightarrow 00:10:53.586$  they bring it from the on state,

NOTE Confidence: 0.698071543428571

 $00:10:53.590 \longrightarrow 00:10:56.950$  which is bound to GTP to the

NOTE Confidence: 0.698071543428571

 $00:10:56.950 \longrightarrow 00:10:59.269$  off state bound to GDP.

NOTE Confidence: 0.698071543428571

 $00:10:59.270 \dashrightarrow 00:11:01.205$  And just to give you a sense of what,

NOTE Confidence: 0.698071543428571

 $00:11:01.210 \longrightarrow 00:11:03.520$  how was this exon impacting the

NOTE Confidence: 0.698071543428571

 $00{:}11{:}03.520 \dashrightarrow 00{:}11{:}05.941$  protein we were seeing that these

NOTE Confidence: 0.698071543428571

 $00:11:05.941 \rightarrow 00:11:08.341$  policy actions were inframe and when

NOTE Confidence: 0.698071543428571

 $00:11:08.341 \rightarrow 00:11:10.928$  they got translated they encoded.

NOTE Confidence: 0.698071543428571

00:11:10.930 --> 00:11:12.156 For prolines,

NOTE Confidence: 0.698071543428571

 $00:11:12.156 \longrightarrow 00:11:15.328$  highly rich proline tails in the

NOTE Confidence: 0.698071543428571

 $00{:}11{:}15{.}328 \dashrightarrow 00{:}11{:}17{.}482$  sea terminus of the parties and

- NOTE Confidence: 0.698071543428571
- $00:11:17.482 \longrightarrow 00:11:20.274$  here is just an example to show
- NOTE Confidence: 0.698071543428571
- $00:11:20.274 \longrightarrow 00:11:22.264$  you that actually these are
- NOTE Confidence: 0.9006125516666667
- $00{:}11{:}22.270 \dashrightarrow 00{:}11{:}24.520$  different molecular weights of the protein.
- NOTE Confidence: 0.9006125516666667
- $00:11:24.520 \longrightarrow 00:11:26.290$  Here is the promoted by
- NOTE Confidence: 0.9006125516666667
- $00:11:26.290 \longrightarrow 00:11:28.070$  P53 with the policy Exxon.
- NOTE Confidence: 0.900612551666667
- $00:11:28.070 \longrightarrow 00:11:29.774$  And here's the repressed
- NOTE Confidence: 0.9006125516666667
- 00:11:29.774 --> 00:11:31.904 P53 isoform of gap 17.
- NOTE Confidence: 0.9006125516666667
- 00:11:31.910 --> 00:11:33.378 Without the policy Axon,
- NOTE Confidence: 0.9006125516666667
- $00:11:33.378 \longrightarrow 00:11:35.580$  so both can be produced and
- NOTE Confidence: 0.900612551666667
- $00:11:35.654 \rightarrow 00:11:37.489$  translated in in the self.
- NOTE Confidence: 0.900612551666667
- $00:11:37.490 \longrightarrow 00:11:39.332$  So at this point we were
- NOTE Confidence: 0.900612551666667
- $00{:}11{:}39{.}332 \dashrightarrow 00{:}11{:}40{.}950$  faced with the question well.
- NOTE Confidence: 0.9006125516666667
- $00{:}11{:}40{.}950 \dashrightarrow 00{:}11{:}45{.}644$  What happens with the CARAS state of either
- NOTE Confidence: 0.9006125516666667
- $00{:}11{:}45{.}644 \dashrightarrow 00{:}11{:}48{.}830$  GTP bound state or GDP bound bound state?
- NOTE Confidence: 0.900612551666667
- $00:11:48.830 \rightarrow 00:11:51.236$  Whenever you have a plus policy
- NOTE Confidence: 0.900612551666667

00:11:51.236 --> 00:11:54.809 gap 17 or a minus policy gap 17,

NOTE Confidence: 0.9006125516666667

 $00:11:54.810 \longrightarrow 00:11:57.750$  and so we did this in cell experiments

NOTE Confidence: 0.900612551666667

 $00:11:57.750 \rightarrow 00:12:00.650$  where we actually first overexpress

NOTE Confidence: 0.900612551666667

 $00:12:00.650 \longrightarrow 00:12:04.575$  either the policy gap 17 or the minus

NOTE Confidence: 0.900612551666667

 $00{:}12{:}04{.}575 \dashrightarrow 00{:}12{:}07{.}676$  policy gap 17 and we actually did a

NOTE Confidence: 0.900612551666667

00:12:07.676 --> 00:12:10.636 pull down to capture GTP bound K rest.

NOTE Confidence: 0.9006125516666667

 $00{:}12{:}10.640 \dashrightarrow 00{:}12{:}11.848$  And then we did.

NOTE Confidence: 0.9006125516666667

 $00:12:11.848 \rightarrow 00:12:14.111$  We used an antibody that it's only

NOTE Confidence: 0.900612551666667

 $00:12:14.111 \rightarrow 00:12:16.415$  recognizing the mutant form of kiras

NOTE Confidence: 0.9006125516666667

 $00{:}12{:}16{.}420 \dashrightarrow 00{:}12{:}20{.}144$  to determine the the levels of

NOTE Confidence: 0.900612551666667

 $00{:}12{:}20{.}144 \dashrightarrow 00{:}12{:}23{.}443$  active cares in these cells and

NOTE Confidence: 0.9006125516666667

 $00:12:23.443 \rightarrow 00:12:25.558$  what we found was interesting,

NOTE Confidence: 0.900612551666667

 $00:12:25.560 \rightarrow 00:12:28.800$  which is in the presence of policy gap 17.

NOTE Confidence: 0.9006125516666667

 $00:12:28.800 \longrightarrow 00:12:30.960$  The isoform promoted by mutant P.

NOTE Confidence: 0.900612551666667

 $00:12:30.960 \longrightarrow 00:12:31.470$  53.

NOTE Confidence: 0.900612551666667

 $00:12:31.470 \longrightarrow 00:12:35.040$  The levels of active care as were

- NOTE Confidence: 0.9006125516666667
- $00:12:35.040 \longrightarrow 00:12:36.060$  actually maintained.
- NOTE Confidence: 0.900612551666667
- 00:12:36.060 --> 00:12:38.508 However, as soon as we overexpress
- NOTE Confidence: 0.900612551666667
- $00:12:38.508 \longrightarrow 00:12:40.810$  the minus policy gap 17 that.
- NOTE Confidence: 0.900612551666667
- $00:12:40.810 \rightarrow 00:12:43.730$  Isoform that is repressed by mutant P 53.
- NOTE Confidence: 0.9006125516666667
- $00{:}12{:}43.730 \dashrightarrow 00{:}12{:}45.907$  We saw that the levels of active
- NOTE Confidence: 0.900612551666667
- $00{:}12{:}45{.}907 \dashrightarrow 00{:}12{:}47{.}873$  care has decreased and also the
- NOTE Confidence: 0.9006125516666667
- $00:12:47.873 \longrightarrow 00:12:49.811$  active levels of Arc which is
- NOTE Confidence: 0.900612551666667
- 00:12:49.811 --> 00:12:51.872 downstream of of cameras were
- NOTE Confidence: 0.9006125516666667
- 00:12:51.872 --> 00:12:53.126 also significantly decreased,
- NOTE Confidence: 0.900612551666667
- $00:12:53.130 \rightarrow 00:12:55.906$  and so it was interesting to see kind
- NOTE Confidence: 0.900612551666667
- $00:12:55.906 \rightarrow 00:12:58.684$  of like the different effects on the
- NOTE Confidence: 0.9006125516666667
- $00:12:58.684 \rightarrow 00:13:01.589$  active form of Keras in the presence
- NOTE Confidence: 0.9006125516666667
- $00:13:01.589 \longrightarrow 00:13:04.466$  or absence of this gap 17 isoforms.
- NOTE Confidence: 0.9006125516666667
- $00{:}13{:}04{.}470 \dashrightarrow 00{:}13{:}06{.}927$  So then we went and did a
- NOTE Confidence: 0.900612551666667
- $00{:}13{:}06{.}927 \dashrightarrow 00{:}13{:}09{.}190$  self free essay where we took
- NOTE Confidence: 0.9006125516666667

 $00:13:09.190 \longrightarrow 00:13:11.030$  while type carrots or mutant.

NOTE Confidence: 0.9006125516666667

 $00:13:11.030 \longrightarrow 00:13:11.818$  The arrest,

NOTE Confidence: 0.900612551666667

 $00{:}13{:}11.818 \dashrightarrow 00{:}13{:}14.576$  and we incubated it with either the

NOTE Confidence: 0.9006125516666667

 $00:13:14.576 \longrightarrow 00:13:17.192$  policy gap 17 or the minus policy gap

NOTE Confidence: 0.900612551666667

00:13:17.192 --> 00:13:20.292 17 and what you can see is that there

NOTE Confidence: 0.9006125516666667

 $00{:}13{:}20.292 \dashrightarrow 00{:}13{:}22.828$  was no much difference in the cell.

NOTE Confidence: 0.9006125516666667

 $00:13:22.828 \rightarrow 00:13:25.460$  Free assays in terms of their capacity

NOTE Confidence: 0.900612551666667

00:13:25.534 --> 00:13:27.819 to hydrolyze GTP bound cameras,

NOTE Confidence: 0.9006125516666667

 $00{:}13{:}27.820 \dashrightarrow 00{:}13{:}30.277$  and this was very odd and surprising

NOTE Confidence: 0.9006125516666667

 $00:13:30.277 \rightarrow 00:13:33.173$  to us because actually in the cells

NOTE Confidence: 0.900612551666667

 $00{:}13{:}33{.}173 \dashrightarrow 00{:}13{:}34{.}941$  they were maintaining different

NOTE Confidence: 0.900612551666667

00:13:34.941 - > 00:13:37.240 levels of Keras bound to GTP.

NOTE Confidence: 0.9006125516666667

 $00:13:37.240 \longrightarrow 00:13:39.400$  So this made us go back to the drawing

NOTE Confidence: 0.9006125516666667

 $00{:}13{:}39{.}400 \dashrightarrow 00{:}13{:}41{.}060$  board and start thinking about.

NOTE Confidence: 0.9006125516666667

00:13:41.060 - 00:13:43.550 What happens in the context of

NOTE Confidence: 0.900612551666667

 $00:13:43.550 \rightarrow 00:13:45.929$  cells in the activity of gaps?

- NOTE Confidence: 0.900612551666667
- $00:13:45.930 \longrightarrow 00:13:48.372$  It turns out that gaps are
- NOTE Confidence: 0.9006125516666667
- $00:13:48.372 \rightarrow 00:13:50.000$  usually cytoplasmic proteins that
- NOTE Confidence: 0.900612551666667
- 00:13:50.067 -> 00:13:52.167 when calls to deactivate Keras,
- NOTE Confidence: 0.9006125516666667
- $00:13:52.170 \longrightarrow 00:13:54.300$  they go to the membrane and
- NOTE Confidence: 0.9006125516666667
- $00{:}13{:}54{.}300 \dashrightarrow 00{:}13{:}56{.}170$  that's when they actually promote
- NOTE Confidence: 0.900612551666667
- $00:13:56.170 \rightarrow 00:13:58.070$  the hydrolysis of the GTP.
- NOTE Confidence: 0.9006125516666667
- $00:13:58.070 \rightarrow 00:14:00.296$  What we were seeing was the following
- NOTE Confidence: 0.900612551666667
- $00:14:00.296 \rightarrow 00:14:02.262$  and the presence of mutant P53.
- NOTE Confidence: 0.900612551666667
- $00:14:02.262 \longrightarrow 00:14:04.734$  When you have the policy gap
- NOTE Confidence: 0.900612551666667
- 00:14:04.734 --> 00:14:05.970 17 being expressed,
- NOTE Confidence: 0.900612551666667
- $00:14:05.970 \longrightarrow 00:14:07.965$  the gap mainly localizes into
- NOTE Confidence: 0.900612551666667
- $00{:}14{:}07{.}965 \dashrightarrow 00{:}14{:}10{.}430$  the title plasm of the cell.
- NOTE Confidence: 0.9006125516666667
- $00:14:10.430 \longrightarrow 00:14:12.074$  Even when we gave it signals
- NOTE Confidence: 0.9006125516666667
- $00{:}14{:}12.074 \dashrightarrow 00{:}14{:}13.850$  to go to the membrane.
- NOTE Confidence: 0.900612551666667
- 00:14:13.850 --> 00:14:15.926 However, when you knock down P.
- NOTE Confidence: 0.9006125516666667

- $00:14:15.930 \longrightarrow 00:14:17.950$  53 out of the cells,
- NOTE Confidence: 0.900612551666667
- $00:14:17.950 \longrightarrow 00:14:21.145$  you can see that there is this the the
- NOTE Confidence: 0.900612551666667
- $00:14:21.145 \rightarrow 00:14:24.730$  gap 17 that is now not expressing policy.
- NOTE Confidence: 0.900612551666667
- 00:14:24.730 --> 00:14:27.736 Exxon now can more likely reach
- NOTE Confidence: 0.900612551666667
- $00:14:27.736 \longrightarrow 00:14:30.376$  the membrane and promote the
- NOTE Confidence: 0.900612551666667
- $00{:}14{:}30{.}376 \dashrightarrow 00{:}14{:}31{.}987$  hydrolysis of Keras.
- NOTE Confidence: 0.9006125516666667
- $00:14:31.990 \longrightarrow 00:14:34.048$  And so we were excited to find
- NOTE Confidence: 0.900612551666667
- $00{:}14{:}34{.}048 \dashrightarrow 00{:}14{:}35{.}681$  these because that led us to
- NOTE Confidence: 0.900612551666667
- $00{:}14{:}35{.}681 \dashrightarrow 00{:}14{:}37{.}277$  a model where we had for the
- NOTE Confidence: 0.8646090091
- $00:14:37.342 \longrightarrow 00:14:39.052$  first time kind of discover
- NOTE Confidence: 0.8646090091
- $00:14:39.052 \rightarrow 00:14:40.762$  how these two owner proteins,
- NOTE Confidence: 0.8646090091
- $00{:}14{:}40.770 \dashrightarrow 00{:}14{:}42.760$  mutant cares and mutant 53
- NOTE Confidence: 0.8646090091
- $00:14:42.760 \longrightarrow 00:14:44.352$  synergizes in the following.
- NOTE Confidence: 0.8646090091
- $00{:}14{:}44{.}360 \dashrightarrow 00{:}14{:}46{.}920$  OK, our model suggests that in the presence
- NOTE Confidence: 0.8646090091
- $00:14:46.920 \rightarrow 00:14:50.115$  of a wild type B 53 or the loss of P53,
- NOTE Confidence: 0.8646090091
- $00:14:50.115 \rightarrow 00:14:52.840$  the cells actually lose policy

- NOTE Confidence: 0.8646090091
- 00:14:52.840 --> 00:14:55.670 axons across multiple M RNA's,
- NOTE Confidence: 0.8646090091
- 00:14:55.670 --> 00:14:58.974 mainly the gap in RNA's and after
- NOTE Confidence: 0.8646090091
- $00{:}14{:}58{.}974 \dashrightarrow 00{:}15{:}01{.}082$  this M RNA gets translated.
- NOTE Confidence: 0.8646090091
- $00:15:01.082 \rightarrow 00:15:03.530$  It encodes gaps that actually are
- NOTE Confidence: 0.8646090091
- $00{:}15{:}03.610 \dashrightarrow 00{:}15{:}06.322$  efficient at reaching the membrane and
- NOTE Confidence: 0.8646090091
- $00{:}15{:}06{.}322 \dashrightarrow 00{:}15{:}09{.}505$  being more efficient at hydrolyzing GTP
- NOTE Confidence: 0.8646090091
- 00:15:09.505 --> 00:15:12.475 bound cameras and promoting tumor growth,
- NOTE Confidence: 0.8646090091
- $00{:}15{:}12{.}480 \dashrightarrow 00{:}15{:}14{.}430$  but not as much as.
- NOTE Confidence: 0.8646090091
- $00{:}15{:}14.430 \dashrightarrow 00{:}15{:}16.128$  When you have the hotspot mutant,
- NOTE Confidence: 0.8646090091
- $00:15:16.130 \longrightarrow 00:15:18.398$  because now this time you are
- NOTE Confidence: 0.8646090091
- $00{:}15{:}18{.}398 \dashrightarrow 00{:}15{:}21{.}126$  gaining a policy Axon and when that
- NOTE Confidence: 0.8646090091
- 00:15:21.126 --> 00:15:23.394 mRNA gets translated it has now
- NOTE Confidence: 0.8646090091
- $00:15:23.394 \rightarrow 00:15:26.339$  these reach domain of prolines that
- NOTE Confidence: 0.8646090091
- $00{:}15{:}26{.}339 \dashrightarrow 00{:}15{:}28{.}824$  prevented from reaching the membrane.
- NOTE Confidence: 0.8646090091
- $00:15:28.830 \longrightarrow 00:15:30.618$  Maintaining an active care
- NOTE Confidence: 0.8646090091

 $00:15:30.618 \rightarrow 00:15:32.853$  estate and more tumor growth.

NOTE Confidence: 0.8646090091

00:15:32.860 --> 00:15:35.191 So just to go back to our model and

NOTE Confidence: 0.8646090091

 $00:15:35.191 \rightarrow 00:15:37.519$  the genetics of pancreatic cancer.

NOTE Confidence: 0.8646090091

 $00:15:37.520 \longrightarrow 00:15:39.606$  So I've told you before that you

NOTE Confidence: 0.8646090091

 $00{:}15{:}39{.}606 \dashrightarrow 00{:}15{:}41{.}761$  needed Karras and mutant P 53 and

NOTE Confidence: 0.8646090091

 $00{:}15{:}41.761 \dashrightarrow 00{:}15{:}43.549$  what our findings had suggested is

NOTE Confidence: 0.8646090091

 $00:15:43.618 \rightarrow 00:15:45.767$  that in the presence of just mutant.

NOTE Confidence: 0.8646090091

 $00:15:45.770 \rightarrow 00:15:48.146$  The rest you still have the active rest,

NOTE Confidence: 0.8646090091

 $00{:}15{:}48{.}150 \dashrightarrow 00{:}15{:}50{.}910$  but then when mutant P 53 comes specifically,

NOTE Confidence: 0.8646090091

 $00:15:50.910 \longrightarrow 00:15:53.314$  the gain of function mutant of P53,

NOTE Confidence: 0.8646090091

00:15:53.314 --> 00:15:56.702 you Now have an altered RNA splicing

NOTE Confidence: 0.8646090091

 $00{:}15{:}56{.}702 \dashrightarrow 00{:}15{:}58{.}996$  and and a feedback loop that now

NOTE Confidence: 0.8646090091

 $00:15:58.996 \rightarrow 00:16:01.030$  prevents the gaps from being active.

NOTE Confidence: 0.8646090091

00:16:01.030 --> 00:16:04.009 And then in this way you can enhance the

NOTE Confidence: 0.8646090091

 $00:16:04.009 \rightarrow 00:16:06.091$  oncogenic signaling and activity of key

NOTE Confidence: 0.8646090091

 $00:16:06.091 \rightarrow 00:16:09.369$  areas and this is our model system currently.

- NOTE Confidence: 0.8646090091
- $00:16:09.370 \longrightarrow 00:16:11.176$  So that was great and we published
- NOTE Confidence: 0.8646090091
- $00:16:11.176 \longrightarrow 00:16:12.709$  this a couple of years ago.
- NOTE Confidence: 0.8646090091
- $00{:}16{:}12.710 \dashrightarrow 00{:}16{:}14.222$  So then we came back into the
- NOTE Confidence: 0.8646090091
- $00:16:14.222 \rightarrow 00:16:15.850$  lab and we started thinking,
- NOTE Confidence: 0.8646090091
- 00:16:15.850 --> 00:16:16.276 well,
- NOTE Confidence: 0.8646090091
- $00{:}16{:}16{.}276 \dashrightarrow 00{:}16{:}18{.}832$  how can we target RNA splicing
- NOTE Confidence: 0.8646090091
- 00:16:18.832 --> 00:16:20.630 and pancreatic cancer cells?
- NOTE Confidence: 0.8646090091
- 00:16:20.630 --> 00:16:22.874 And so recently,
- NOTE Confidence: 0.8646090091
- $00{:}16{:}22.874 \dashrightarrow 00{:}16{:}25.866$  this small molecule compound,
- NOTE Confidence: 0.8646090091
- $00{:}16{:}25{.}870 \dashrightarrow 00{:}16{:}28{.}607$  H3 B 8800 it started being tested
- NOTE Confidence: 0.8646090091
- $00:16:28.607 \rightarrow 00:16:31.229$  in phase one clinical trials,
- NOTE Confidence: 0.8646090091
- 00:16:31.230 --> 00:16:34.541 and they got interested in our research
- NOTE Confidence: 0.8646090091
- $00:16:34.541 \dashrightarrow 00:16:37.160$  with pancreatic cancer and mutant 53.
- NOTE Confidence: 0.8646090091
- $00:16:37.160 \longrightarrow 00:16:39.610$  So basically what H3 B 8800 does.
- NOTE Confidence: 0.8646090091
- $00:16:39.610 \longrightarrow 00:16:41.140$  It binds to one of the.
- NOTE Confidence: 0.8646090091

 $00:16:41.140 \longrightarrow 00:16:44.020$  Course splicing proteins as F3V1 and

NOTE Confidence: 0.8646090091

 $00{:}16{:}44.020 \dashrightarrow 00{:}16{:}46.428$  prevents this whole machinery the

NOTE Confidence: 0.8646090091

 $00{:}16{:}46{.}428 \dashrightarrow 00{:}16{:}48{.}463$  spliceosome to bind and recognize

NOTE Confidence: 0.8646090091

00:16:48.463 --> 00:16:51.160 fully the M RNA's, and so we were.

NOTE Confidence: 0.8646090091

00:16:51.160 --> 00:16:52.220 Our hypothesis was well,

NOTE Confidence: 0.8646090091

 $00:16:52.220 \longrightarrow 00:16:54.280$  if mutant P53 tumors really

NOTE Confidence: 0.8646090091

00:16:54.280 --> 00:16:56.340 depend on ultra RNA splicing,

NOTE Confidence: 0.8646090091

 $00:16:56.340 \rightarrow 00:16:58.476$  they'd be more sensitive to toddler.

NOTE Confidence: 0.8646090091

00:16:58.480 --> 00:17:00.930 They would be more sensitive

NOTE Confidence: 0.8646090091

 $00:17:00.930 \longrightarrow 00:17:03.380$  to any perturbation into the

NOTE Confidence: 0.8646090091

00:17:03.471 -> 00:17:06.472 splicing machinery with the AD 800,

NOTE Confidence: 0.8646090091

 $00{:}17{:}06{.}472 \dashrightarrow 00{:}17{:}09{.}130$  so we launched what we call a

NOTE Confidence: 0.8646090091

 $00{:}17{:}09{.}130 \dashrightarrow 00{:}17{:}11{.}464$  mouse trial where we took mice.

NOTE Confidence: 0.8646090091

 $00:17:11.470 \longrightarrow 00:17:14.458$  That either had tumors that had

NOTE Confidence: 0.8646090091

00:17:14.458 --> 00:17:16.958 mutant P53 in them, so that's red,

NOTE Confidence: 0.8646090091

 $00:17:16.960 \longrightarrow 00:17:19.528$  or that lacked mutant 53 in one

- NOTE Confidence: 0.8646090091
- $00:17:19.528 \longrightarrow 00:17:20.812$  which are blue.
- NOTE Confidence: 0.8646090091
- $00:17:20.820 \longrightarrow 00:17:23.442$  And then we randomize these animals
- NOTE Confidence: 0.8646090091
- $00:17:23.442 \longrightarrow 00:17:25.939$  to either receive 8800 or vehicle.
- NOTE Confidence: 0.8646090091
- $00:17:25.939 \longrightarrow 00:17:28.297$  And what you can appreciate is
- NOTE Confidence: 0.8646090091
- $00{:}17{:}28{.}297 \dashrightarrow 00{:}17{:}29{.}979$  that the solid lines,
- NOTE Confidence: 0.8646090091
- $00:17:29.980 \longrightarrow 00:17:32.256$  which are the animals that receive 8800,
- NOTE Confidence: 0.8646090091
- $00:17:32.256 \longrightarrow 00:17:34.536$  they all benefited from having
- NOTE Confidence: 0.8646090091
- $00:17:34.536 \longrightarrow 00:17:36.360$  from receiving the compound.
- NOTE Confidence: 0.8646090091
- 00:17:36.360 --> 00:17:36.753 However,
- NOTE Confidence: 0.8646090091
- $00:17:36.753 \longrightarrow 00:17:38.718$  the animals that survive and
- NOTE Confidence: 0.8646090091
- $00{:}17{:}38{.}718 \dashrightarrow 00{:}17{:}40{.}697$  benefited the most were those
- NOTE Confidence: 0.8646090091
- $00{:}17{:}40.697 \dashrightarrow 00{:}17{:}43.174$  ones that had mutant P53 in them,
- NOTE Confidence: 0.8646090091
- $00{:}17{:}43.174 \dashrightarrow 00{:}17{:}44.686$  suggesting that these mutations
- NOTE Confidence: 0.8646090091
- $00{:}17{:}44.686 \dashrightarrow 00{:}17{:}45.820$  sensitizes these tumors.
- NOTE Confidence: 0.8646090091
- $00:17:45.820 \longrightarrow 00:17:48.480$  To this lysine modulator.
- NOTE Confidence: 0.8646090091

00:17:48.480 --> 00:17:51.600 And when we did RNA splicing

NOTE Confidence: 0.8646090091

 $00{:}17{:}51.600 \dashrightarrow 00{:}17{:}53.606$  analysis and after we treated

NOTE Confidence: 0.8646090091

 $00:17:53.606 \longrightarrow 00:17:55.420$  these tumors with the 8800,

NOTE Confidence: 0.8646090091

 $00:17:55.420 \longrightarrow 00:17:58.020$  we can nicely see how.

NOTE Confidence: 0.832197701666667

 $00{:}17{:}58{.}020 \dashrightarrow 00{:}18{:}00{.}174$  H3 B 8800 was repressing the

NOTE Confidence: 0.832197701666667

 $00{:}18{:}00{.}174 \dashrightarrow 00{:}18{:}02{.}600$  retention of that policy Axon in the

NOTE Confidence: 0.8321977016666667

 $00:18:02.600 \longrightarrow 00:18:04.735$  cells in a function as a function

NOTE Confidence: 0.832197701666667

 $00:18:04.806 \rightarrow 00:18:06.910$  depending on the concentration.

NOTE Confidence: 0.832197701666667

 $00:18:06.910 \longrightarrow 00:18:08.590$  So you know other words.

NOTE Confidence: 0.832197701666667

 $00:18:08.590 \rightarrow 00:18:10.822$  This compound was reversing the key

NOTE Confidence: 0.832197701666667

 $00{:}18{:}10.822 \dashrightarrow 00{:}18{:}12.966$  splicing events that we had seen

NOTE Confidence: 0.8321977016666667

 $00:18:12.966 \rightarrow 00:18:15.094$  in the presence of mutant P. 53.

NOTE Confidence: 0.832197701666667

 $00{:}18{:}15{.}094 \dashrightarrow 00{:}18{:}17{.}712$  Lastly, we have now established a human

NOTE Confidence: 0.8321977016666667

 $00:18:17.712 \longrightarrow 00:18:20.608$  model where we have isogenix cells that

NOTE Confidence: 0.832197701666667

 $00:18:20.608 \rightarrow 00:18:22.890$  express different forms of mutant P.

NOTE Confidence: 0.832197701666667

 $00:18:22.890 \longrightarrow 00:18:24.766$  53 and we know that when we

- NOTE Confidence: 0.832197701666667
- $00:18:24.766 \longrightarrow 00:18:26.510$  treat them with this compound,
- NOTE Confidence: 0.8321977016666667
- 00:18:26.510 --> 00:18:28.900 the mutants and particularly are
- NOTE Confidence: 0.8321977016666667
- $00{:}18{:}28{.}900 \dashrightarrow 00{:}18{:}31{.}290$  more sensitive to these compounds
- NOTE Confidence: 0.832197701666667
- $00:18:31.290 \longrightarrow 00:18:33.084$  when you compare them to the
- NOTE Confidence: 0.8321977016666667
- $00{:}18{:}33{.}084 \dashrightarrow 00{:}18{:}34{.}802$  counterparts when they don't have P53
- NOTE Confidence: 0.832197701666667
- $00:18:34.802 \rightarrow 00:18:36.877$  or when they have a wild type P53.
- NOTE Confidence: 0.832197701666667
- $00{:}18{:}36{.}877 \dashrightarrow 00{:}18{:}38{.}719$  So based on these results we
- NOTE Confidence: 0.8321977016666667
- 00:18:38.719 --> 00:18:41.108 are now in discussions with HB,
- NOTE Confidence: 0.8321977016666667
- 00:18:41.110 --> 00:18:44.430 biomedicine and row Invad sciences,
- NOTE Confidence: 0.832197701666667
- $00:18:44.430 \longrightarrow 00:18:46.350$  who recently bought the 88.
- NOTE Confidence: 0.832197701666667
- 00:18:46.350 --> 00:18:47.685 100 compound because we would
- NOTE Confidence: 0.832197701666667
- $00{:}18{:}47.685 \dashrightarrow 00{:}18{:}49.020$  like to start a phase.
- NOTE Confidence: 0.8321977016666667
- $00:18:49.020 \longrightarrow 00:18:50.580$  Two clinical trial where
- NOTE Confidence: 0.8321977016666667
- 00:18:50.580 --> 00:18:52.140 we combine Gemma Broxton,
- NOTE Confidence: 0.832197701666667
- $00:18:52.140 \longrightarrow 00:18:53.568$  which is one of the first
- NOTE Confidence: 0.832197701666667

00:18:53.568 --> 00:18:54.520 gamma standard of care,

NOTE Confidence: 0.8321977016666667

 $00:18:54.520 \rightarrow 00:18:56.660$  chemotherapeutic lines for pancreatic

NOTE Confidence: 0.8321977016666667

 $00:18:56.660 \rightarrow 00:18:59.335$  cancer patients and start escalating

NOTE Confidence: 0.832197701666667

 $00{:}18{:}59{.}335 \dashrightarrow 00{:}19{:}01{.}696$  doses of 8800 for patients whose

NOTE Confidence: 0.832197701666667

 $00:19:01.696 \rightarrow 00:19:03.716$  tumors have gained a function.

NOTE Confidence: 0.832197701666667

00:19:03.720 --> 00:19:06.168 Mutant of P 53 so hopefully

NOTE Confidence: 0.8321977016666667

 $00:19:06.168 \longrightarrow 00:19:08.340$  we can launch this soon.

NOTE Confidence: 0.832197701666667

 $00{:}19{:}08{.}340 \dashrightarrow 00{:}19{:}09{.}270$  So let's back.

NOTE Confidence: 0.8321977016666667

 $00:19:09.270 \longrightarrow 00:19:11.942$  Let's go back to you know what are

NOTE Confidence: 0.832197701666667

 $00:19:11.942 \rightarrow 00:19:14.540$  the mutations that Dr pancreatic cancer?

NOTE Confidence: 0.832197701666667

 $00:19:14.540 \longrightarrow 00:19:15.748$  What have we understood

NOTE Confidence: 0.832197701666667

 $00:19:15.748 \rightarrow 00:19:17.258$  and how can we target?

NOTE Confidence: 0.832197701666667

00:19:17.260 --> 00:19:19.508 To drive personalized medicine,

NOTE Confidence: 0.8321977016666667

 $00:19:19.508 \longrightarrow 00:19:20.070$  so,

NOTE Confidence: 0.832197701666667

00:19:20.070 --> 00:19:21.622 as I mentioned before,

NOTE Confidence: 0.832197701666667

 $00{:}19{:}21.622 \dashrightarrow 00{:}19{:}23.562$  we now understand that KIERAS

- NOTE Confidence: 0.832197701666667
- 00:19:23.562 --> 00:19:25.393 mutations are the most common
- NOTE Confidence: 0.832197701666667
- 00:19:25.393 > 00:19:27.113 mutations and they are required
- NOTE Confidence: 0.832197701666667
- $00:19:27.113 \longrightarrow 00:19:29.030$  hit mutation to form tumors.
- NOTE Confidence: 0.8321977016666667
- $00:19:29.030 \longrightarrow 00:19:31.918$  We know that 10% of the cases have
- NOTE Confidence: 0.8321977016666667
- 00:19:31.918 --> 00:19:33.368 familiar pancreatic cancer and
- NOTE Confidence: 0.832197701666667
- $00{:}19{:}33.368 \dashrightarrow 00{:}19{:}35.664$  most of them have mutations in ATM
- NOTE Confidence: 0.832197701666667
- $00:19:35.664 \rightarrow 00:19:38.134$  and when they have these mutations
- NOTE Confidence: 0.8321977016666667
- 00:19:38.134 --> 00:19:40.209 they are giving PARP inhibitors
- NOTE Confidence: 0.8321977016666667
- $00{:}19{:}40{.}210 \dashrightarrow 00{:}19{:}43{.}126$  and that's why we do molecular
- NOTE Confidence: 0.832197701666667
- $00:19:43.130 \longrightarrow 00:19:44.790$  molecular profiling industry rumors
- NOTE Confidence: 0.832197701666667
- $00:19:44.790 \longrightarrow 00:19:47.280$  to identify this cohort of patients.
- NOTE Confidence: 0.832197701666667
- $00{:}19{:}47.280 \dashrightarrow 00{:}19{:}49.624$  To have actionable mutations.
- NOTE Confidence: 0.8321977016666667
- $00:19:49.624 \longrightarrow 00:19:51.968$  We also know that,
- NOTE Confidence: 0.8321977016666667
- 00:19:51.970 --> 00:19:53.394 as I mentioned before,
- NOTE Confidence: 0.8321977016666667
- $00{:}19{:}53{.}394 \dashrightarrow 00{:}19{:}56{.}110$  that 30% of the sporadic pancreatic tumors,
- NOTE Confidence: 0.832197701666667

 $00:19:56.110 \longrightarrow 00:19:58.448$  which are the most common ones are

NOTE Confidence: 0.832197701666667

 $00:19:58.448 \longrightarrow 00:20:00.673$  driven by gain of function 53.

NOTE Confidence: 0.832197701666667

00:20:00.673 --> 00:20:02.688 And as I mentioned before,

NOTE Confidence: 0.8321977016666667

 $00:20:02.690 \rightarrow 00:20:05.012$  we're hoping to start a clinical

NOTE Confidence: 0.832197701666667

 $00:20:05.012 \longrightarrow 00:20:06.218$  trial using 8800.

NOTE Confidence: 0.832197701666667

 $00{:}20{:}06{.}218 \dashrightarrow 00{:}20{:}08{.}786$  These glycine inhibitors to see if

NOTE Confidence: 0.832197701666667

 $00:20:08.786 \longrightarrow 00:20:11.711$  we can bring a targeted therapy

NOTE Confidence: 0.8321977016666667

00:20:11.711 -> 00:20:13.787 for these sporadic tumors.

NOTE Confidence: 0.832197701666667

00:20:13.790 --> 00:20:15.974 Now we're still facing the challenge

NOTE Confidence: 0.832197701666667

 $00{:}20{:}15{.}974 \dashrightarrow 00{:}20{:}18{.}210$  that we still don't understand.

NOTE Confidence: 0.832197701666667

 $00:20:18.210 \longrightarrow 00:20:20.320$  30. What is the mutation?

NOTE Confidence: 0.832197701666667

 $00:20:20.320 \longrightarrow 00:20:23.035$  That drives the other 30% of

NOTE Confidence: 0.832197701666667

00:20:23.035 --> 00:20:25.610 pancreatic tumors because we also,

NOTE Confidence: 0.8321977016666667

 $00:20:25.610 \longrightarrow 00:20:27.591$  because we already know that the other

NOTE Confidence: 0.832197701666667

 $00:20:27.591 \rightarrow 00:20:30.015 30\%$  is driven by loss of function P.

NOTE Confidence: 0.8321977016666667

 $00:20:30.020 \longrightarrow 00:20:30.311$  53.
- NOTE Confidence: 0.832197701666667
- $00:20:30.311 \longrightarrow 00:20:32.057$  So for these two last groups.
- NOTE Confidence: 0.832197701666667
- 00:20:32.060 --> 00:20:32.457 Unfortunately,
- NOTE Confidence: 0.832197701666667
- $00:20:32.457 \rightarrow 00:20:35.633$  right now we don't have any targeted therapy
- NOTE Confidence: 0.832197701666667
- $00:20:35.633 \rightarrow 00:20:38.718$  or any trials that are going to launch here,
- NOTE Confidence: 0.8321977016666667
- $00{:}20{:}38.720 \dashrightarrow 00{:}20{:}40.496$  so we were curious to know
- NOTE Confidence: 0.832197701666667
- $00:20:40.496 \longrightarrow 00:20:41.680$  well what is sporadic,
- NOTE Confidence: 0.832197701666667
- $00:20:41.680 \rightarrow 00:20:44.068$  what other mutations, Dr,
- NOTE Confidence: 0.832197701666667
- 00:20:44.068 --> 00:20:47.053 sporadic tumors of pancreatic cancer,
- NOTE Confidence: 0.8321977016666667
- $00:20:47.060 \longrightarrow 00:20:49.022$  and so to answer that question
- NOTE Confidence: 0.832197701666667
- $00:20:49.022 \longrightarrow 00:20:50.330$  I mentioned before that.
- NOTE Confidence: 0.832197701666667
- $00:20:50.330 \longrightarrow 00:20:52.946$  You know there is a such a a
- NOTE Confidence: 0.832197701666667
- $00:20:52.946 \longrightarrow 00:20:55.026$  large number of mutations that
- NOTE Confidence: 0.832197701666667
- $00:20:55.026 \longrightarrow 00:20:57.750$  appear in very low frequencies,
- NOTE Confidence: 0.832197701666667
- $00:20:57.750 \longrightarrow 00:20:59.798$  but it's hard to study each one of
- NOTE Confidence: 0.832197701666667
- $00{:}20{:}59{.}798 \dashrightarrow 00{:}21{:}01{.}338$  these mutations to understand well.
- NOTE Confidence: 0.8321977016666667

 $00:21:01.340 \longrightarrow 00:21:03.355$  Are they driver mutations or

NOTE Confidence: 0.832197701666667

 $00:21:03.355 \longrightarrow 00:21:04.967$  are they passenger mutations?

NOTE Confidence: 0.832197701666667

 $00{:}21{:}04{.}970 \dashrightarrow 00{:}21{:}06{.}854$  And so we took an inform

NOTE Confidence: 0.8321977016666667

 $00:21:06.854 \rightarrow 00:21:08.110$  approach where we went

NOTE Confidence: 0.8599037

 $00:21:08.178 \dashrightarrow 00:21:10.446$  back to the basic contact concept.

NOTE Confidence: 0.8599037

00:21:10.450 --> 00:21:11.962 Sorry of mutual esclusiva,

NOTE Confidence: 0.8599037

 $00:21:11.962 \rightarrow 00:21:15.190$  so just to remind everyone we know that

NOTE Confidence: 0.8599037

 $00:21:15.190 \rightarrow 00:21:17.410$  mutations may be mutually exclusive,

NOTE Confidence: 0.8599037

 $00{:}21{:}17{.}410 \dashrightarrow 00{:}21{:}20{.}338$  meaning that if P53 is present.

NOTE Confidence: 0.8599037

 $00:21:20.340 \longrightarrow 00:21:22.398$  The mutation in P53 is present,

NOTE Confidence: 0.8599037

 $00{:}21{:}22{.}400 \dashrightarrow 00{:}21{:}25{.}433$  then it would turn into a viable tumor cell.

NOTE Confidence: 0.8599037

00:21:25.440 --> 00:21:28.420 If other mutation is present but not P53,

NOTE Confidence: 0.8599037

 $00:21:28.420 \longrightarrow 00:21:29.460$  it could be viable,

NOTE Confidence: 0.8599037

 $00{:}21{:}29{.}460 \dashrightarrow 00{:}21{:}31{.}116$  but if both mutations are present,

NOTE Confidence: 0.8599037

00:21:31.120 --> 00:21:32.860 it could be synthetic, lethal,

NOTE Confidence: 0.8599037

 $00:21:32.860 \rightarrow 00:21:35.182$  and the mutual exclusivity of these

- NOTE Confidence: 0.8599037
- $00{:}21{:}35{.}182 \dashrightarrow 00{:}21{:}37{.}550$  mutations is because sometimes these mutual

 $00{:}21{:}37{.}550 \dashrightarrow 00{:}21{:}39{.}836$  exclusive mutations either have the same

NOTE Confidence: 0.8599037

 $00{:}21{:}39{.}836 \dashrightarrow 00{:}21{:}42{.}328$  function or impact the same pathway and

NOTE Confidence: 0.8599037

 $00{:}21{:}42{.}328$  -->  $00{:}21{:}44{.}460$  that's what makes them driver mutations.

NOTE Confidence: 0.8599037

 $00{:}21{:}44.460 \dashrightarrow 00{:}21{:}47.680$  So we started conducting a mutual exclusivity

NOTE Confidence: 0.8599037

 $00{:}21{:}47.680 \dashrightarrow 00{:}21{:}50.159$  analysis by taking advantage of C.

NOTE Confidence: 0.8599037

 $00:21:50.160 \longrightarrow 00:21:50.910$  Bioportal.

NOTE Confidence: 0.8599037

 $00:21:50.910 \longrightarrow 00:21:53.160$  Which has the.

NOTE Confidence: 0.8599037

00:21:53.160 --> 00:21:56.100 Mutation signatures of over 3000

NOTE Confidence: 0.8599037

 $00:21:56.100 \rightarrow 00:21:59.040$  patient samples of pancreatic cancer,

NOTE Confidence: 0.8599037

 $00{:}21{:}59{.}040 \dashrightarrow 00{:}22{:}01{.}084$  and so the 1st results that we

NOTE Confidence: 0.8599037

00:22:01.084 --> 00:22:03.046 derive from this analysis are are

NOTE Confidence: 0.8599037

 $00:22:03.046 \longrightarrow 00:22:05.080$  shown here in this volcano plot.

NOTE Confidence: 0.8599037

 $00{:}22{:}05{.}080 \dashrightarrow 00{:}22{:}07{.}555$  So on the right hand side we have the

NOTE Confidence: 0.8599037

 $00{:}22{:}07{.}555 \dashrightarrow 00{:}22{:}09{.}535$  mutations that Co occur with mutant P.

 $00:22:09.540 \longrightarrow 00:22:11.380$  53 and in the left hand side we

NOTE Confidence: 0.8599037

 $00{:}22{:}11{.}380 \dashrightarrow 00{:}22{:}13{.}481$  have the mutations that are mutually

NOTE Confidence: 0.8599037

00:22:13.481 --> 00:22:15.605 exclusive for P53 and this was the

NOTE Confidence: 0.8599037

 $00{:}22{:}15.605 \dashrightarrow 00{:}22{:}17.714$  side of the volcano that we were

NOTE Confidence: 0.8599037

 $00:22:17.714 \longrightarrow 00:22:19.494$  interested in because this potentially

NOTE Confidence: 0.8599037

 $00{:}22{:}19{.}494 \dashrightarrow 00{:}22{:}21{.}793$  could tell us what mutations were

NOTE Confidence: 0.8599037

 $00:22:21.793 \rightarrow 00:22:24.127$  driving this disease aside from mutant.

NOTE Confidence: 0.8599037

 $00:22:24.130 \longrightarrow 00:22:27.208$  53 so as a sa proof of concept,

NOTE Confidence: 0.8599037

 $00{:}22{:}27{.}210 \dashrightarrow 00{:}22{:}28{.}794$  key results in the middle is

NOTE Confidence: 0.8599037

 $00:22:28.794 \longrightarrow 00:22:29.586$  the first mutation.

NOTE Confidence: 0.8599037

 $00:22:29.590 \longrightarrow 00:22:31.508$  It appears for all of the tumors,

NOTE Confidence: 0.8599037

 $00:22:31.510 \rightarrow 00:22:34.046$  but here's where it got surprising to us.

NOTE Confidence: 0.8599037

 $00:22:34.050 \rightarrow 00:22:36.120$  One of the most mutually exclusive

NOTE Confidence: 0.8599037

00:22:36.120 --> 00:22:39.450 mutations to P53 was mutation in SF3B1.

NOTE Confidence: 0.8599037

 $00:22:39.450 \longrightarrow 00:22:42.310$  It's a score splicing protein.

NOTE Confidence: 0.8599037

 $00:22:42.310 \longrightarrow 00:22:44.907$  Then it on this same side we

- NOTE Confidence: 0.8599037
- 00:22:44.907 --> 00:22:46.669 have mutations in RBM 10,

 $00{:}22{:}46.670 \dashrightarrow 00{:}22{:}49.210$  which is another splicing factor.

NOTE Confidence: 0.8599037

 $00:22:49.210 \longrightarrow 00:22:50.935$  But on the core occurring

NOTE Confidence: 0.8599037

 $00:22:50.935 \longrightarrow 00:22:52.610$  side we had a U2AF1,

NOTE Confidence: 0.8599037

 $00:22:52.610 \longrightarrow 00:22:54.060$  again another mutation in another.

NOTE Confidence: 0.8599037

00:22:54.060 --> 00:22:54.850 License factor,

NOTE Confidence: 0.8599037

 $00:22:54.850 \rightarrow 00:22:57.220$  so if our hypothesis was true,

NOTE Confidence: 0.8599037

 $00:22:57.220 \longrightarrow 00:22:58.999$  it's potentially that

NOTE Confidence: 0.8599037

 $00{:}22{:}58{.}999 \dashrightarrow 00{:}23{:}00{.}778$  mutually exclusive mutations,

NOTE Confidence: 0.8599037

 $00{:}23{:}00{.}780 \dashrightarrow 00{:}23{:}03{.}972$  meaning S3B1 and RBM 10 could be

NOTE Confidence: 0.8599037

 $00{:}23{:}03{.}972 \dashrightarrow 00{:}23{:}06{.}918$  drivers of pancreatic cancer and just

NOTE Confidence: 0.8599037

00:23:06.918 --> 00:23:09.906 assuming what type of mutations are

NOTE Confidence: 0.8599037

 $00{:}23{:}09{.}906 \dashrightarrow 00{:}23{:}12{.}520$  present in S4B1S4B1 in pancreatic

NOTE Confidence: 0.8599037

00:23:12.520 --> 00:23:15.620 cancer has a driver mutation.

NOTE Confidence: 0.8599037

 $00:23:15.620 \longrightarrow 00:23:17.804$  Very hot spot mutation in case 700.

00:23:17.810 --> 00:23:21.464 E RBM 10 is mainly truncating mutation.

NOTE Confidence: 0.8599037

00:23:21.470 - 00:23:23.690 So basically you're losing the

NOTE Confidence: 0.8599037

 $00{:}23{:}23{.}690 \dashrightarrow 00{:}23{:}26{.}982$  function of RBM 10 and U2AF1 has

NOTE Confidence: 0.8599037

00:23:26.982 --> 00:23:29.566 a hotspot mutation in S34F.

NOTE Confidence: 0.8599037

 $00:23:29.566 \longrightarrow 00:23:31.746$  So we our question was,

NOTE Confidence: 0.8599037

 $00{:}23{:}31.750 \dashrightarrow 00{:}23{:}34.216$  are any of these three mutations

NOTE Confidence: 0.8599037

00:23:34.216 --> 00:23:35.449 driving pancreatic cancer?

NOTE Confidence: 0.8599037

 $00:23:35.450 \longrightarrow 00:23:38.201$  And so we took advantage and we

NOTE Confidence: 0.8599037

 $00{:}23{:}38{.}201 \dashrightarrow 00{:}23{:}39{.}380$  started generating genetically

NOTE Confidence: 0.8599037

 $00:23:39.447 \longrightarrow 00:23:40.968$  engineered mouse models.

NOTE Confidence: 0.8599037

 $00{:}23{:}40{.}970 \dashrightarrow 00{:}23{:}42{.}430$  So here's the case.

NOTE Confidence: 0.8599037

 $00:23:42.430 \longrightarrow 00:23:44.620$  C model system where it's only

NOTE Confidence: 0.8599037

00:23:44.699 - 00:23:46.599 driven by ACARAS mutation.

NOTE Confidence: 0.8599037

 $00:23:46.600 \longrightarrow 00:23:48.532$  And what we found and what we

NOTE Confidence: 0.8599037

 $00{:}23{:}48{.}532 \dashrightarrow 00{:}23{:}50{.}215$  expected was that these animals

NOTE Confidence: 0.8599037

 $00:23:50.215 \longrightarrow 00:23:52.185$  should only form pannings or

- NOTE Confidence: 0.8599037
- 00:23:52.185 --> 00:23:54.080 pancreatic and triphenyl neoplasias,

 $00:23:54.080 \longrightarrow 00:23:55.724$  those precancer states.

NOTE Confidence: 0.8599037

 $00{:}23{:}55{.}724 \dashrightarrow 00{:}24{:}00{.}260$  So then we cross this KC animal with a

NOTE Confidence: 0.8599037

 $00:24:00.260 \rightarrow 00:24:03.530$  U2AF1 mutant animal for the S34F mutation.

NOTE Confidence: 0.8599037

 $00{:}24{:}03{.}530 \dashrightarrow 00{:}24{:}05{.}600$  And what we found is that

NOTE Confidence: 0.8599037

 $00{:}24{:}05{.}600 \dashrightarrow 00{:}24{:}07{.}180$  actually there are pannings,

NOTE Confidence: 0.8599037

 $00:24:07.180 \longrightarrow 00:24:09.196$  but not as much as we expected.

NOTE Confidence: 0.8599037

 $00:24:09.200 \rightarrow 00:24:10.349$  And most importantly,

NOTE Confidence: 0.8599037

 $00{:}24{:}10{.}349 \dashrightarrow 00{:}24{:}13{.}030$  there was no Peacock in these animals.

NOTE Confidence: 0.8599037

00:24:13.030 --> 00:24:13.932 But surprisingly,

NOTE Confidence: 0.8599037

 $00:24:13.932 \longrightarrow 00:24:16.187$  the animals that had them,

NOTE Confidence: 0.8599037

 $00{:}24{:}16{.}190 \dashrightarrow 00{:}24{:}19{.}446$  the Keras mutation and the SFRB 1 mutation,

NOTE Confidence: 0.8599037

00:24:19.450 --> 00:24:21.046 for eign pancreatic tumors,

NOTE Confidence: 0.8599037

 $00{:}24{:}21.046 \dashrightarrow 00{:}24{:}25.748$  same as the animals that we cross to have K,

NOTE Confidence: 0.8599037

 $00:24:25.750 \rightarrow 00:24:26.266$  res,

 $00{:}24{:}26{.}266 \dashrightarrow 00{:}24{:}28{.}330$  and RBM ten loss.

NOTE Confidence: 0.765729881111111

 $00{:}24{:}28{.}330 \dashrightarrow 00{:}24{:}30{.}320$  So here's just the quantification

NOTE Confidence: 0.765729881111111

 $00:24:30.320 \longrightarrow 00:24:31.912$  done by our pathologist,

NOTE Confidence: 0.765729881111111

 $00{:}24{:}31{.}920 \dashrightarrow 00{:}24{:}34{.}269$  who you can see that there is only pdac

NOTE Confidence: 0.765729881111111

 $00{:}24{:}34{.}269 \dashrightarrow 00{:}24{:}36{.}578$  and the animals that have the nutrition

NOTE Confidence: 0.765729881111111

 $00{:}24{:}36{.}578 \dashrightarrow 00{:}24{:}38{.}527$  in S4B1 and the nutrition in our BM.

NOTE Confidence: 0.76572988111111

 $00:24:38.530 \longrightarrow 00:24:41.034$  10 There is more pannings also in these

NOTE Confidence: 0.76572988111111

 $00:24:41.034 \rightarrow 00:24:43.448$  animals and they succumb to the disease.

NOTE Confidence: 0.765729881111111

 $00{:}24{:}43.450 \dashrightarrow 00{:}24{:}44.677$  Very early on,

NOTE Confidence: 0.765729881111111

00:24:44.677 - 00:24:47.540 so we are now in this hypothesis

NOTE Confidence: 0.765729881111111

 $00{:}24{:}47.633 \dashrightarrow 00{:}24{:}51.377$  that we're trying to further test which is.

NOTE Confidence: 0.76572988111111

 $00{:}24{:}51{.}380 \dashrightarrow 00{:}24{:}54{.}092$  We believe now that pancreatic cancer

NOTE Confidence: 0.765729881111111

 $00{:}24{:}54.092 \dashrightarrow 00{:}24{:}56.980$  cells that have a mutant carras

NOTE Confidence: 0.765729881111111

 $00:24:56.980 \rightarrow 00:24:59.450$  actually require a splicing switch

NOTE Confidence: 0.765729881111111

 $00:24:59.450 \rightarrow 00:25:02.578$  in order to become tumor cells,

NOTE Confidence: 0.76572988111111

 $00:25:02.580 \longrightarrow 00:25:04.515$  and most likely the majority

- NOTE Confidence: 0.765729881111111
- $00:25:04.515 \longrightarrow 00:25:06.946$  of these of these tumors will

00:25:06.946 --> 00:25:08.992 develop through a mutant P53,

NOTE Confidence: 0.765729881111111

 $00:25:08.992 \longrightarrow 00:25:11.456$  which I showed you before how it

NOTE Confidence: 0.765729881111111

00:25:11.456 --> 00:25:13.039 drives alternative RNA splicing,

NOTE Confidence: 0.765729881111111

 $00:25:13.040 \longrightarrow 00:25:15.600$  but we're now fathering.

NOTE Confidence: 0.765729881111111

00:25:15.600 --> 00:25:19.681 Starting how these SF 3B1 mutation,

NOTE Confidence: 0.76572988111111

 $00{:}25{:}19.681 \dashrightarrow 00{:}25{:}23.069$  and RBM ten loss also drive the the

NOTE Confidence: 0.765729881111111

 $00:25:23.069 \rightarrow 00:25:26.254$  the disease based on a splicing change,

NOTE Confidence: 0.765729881111111

 $00:25:26.260 \rightarrow 00:25:29.266$  and these animals are now being

NOTE Confidence: 0.765729881111111

00:25:29.266 --> 00:25:31.865 characterized by a couple of

NOTE Confidence: 0.76572988111111

00:25:31.865 --> 00:25:34.355 postdoctoral fellows in my lab,

NOTE Confidence: 0.76572988111111

 $00:25:34.360 \longrightarrow 00:25:36.584$  and so I just want to quickly mention

NOTE Confidence: 0.765729881111111

 $00:25:36.584 \longrightarrow 00:25:38.289$  that they have obtained really

NOTE Confidence: 0.765729881111111

 $00{:}25{:}38{.}289 \dashrightarrow 00{:}25{:}40{.}094$  interesting results in terms of

NOTE Confidence: 0.76572988111111

 $00{:}25{:}40.094 \dashrightarrow 00{:}25{:}42.350$  what are the splicing defects that

 $00:25:42.350 \rightarrow 00:25:44.220$  these proteins mutated proteins.

NOTE Confidence: 0.765729881111111

 $00{:}25{:}44{.}220 \dashrightarrow 00{:}25{:}45{.}720$  Are leading to.

NOTE Confidence: 0.76572988111111

 $00:25:45.720 \longrightarrow 00:25:48.420$  They are very similar to the

NOTE Confidence: 0.76572988111111

 $00:25:48.420 \longrightarrow 00:25:49.722$  P53 splicing changes.

NOTE Confidence: 0.765729881111111

 $00{:}25{:}49{.}722 \dashrightarrow 00{:}25{:}52{.}760$  We do tons of deep RNA sequencing

NOTE Confidence: 0.765729881111111

 $00{:}25{:}52{.}844 \dashrightarrow 00{:}25{:}54{.}740$  into this model systems.

NOTE Confidence: 0.765729881111111

 $00{:}25{:}54{.}740 \dashrightarrow 00{:}25{:}56{.}051$  We do several.

NOTE Confidence: 0.765729881111111

 $00{:}25{:}56.051 \dashrightarrow 00{:}25{:}58.236$  We run several algorithms to

NOTE Confidence: 0.765729881111111

 $00:25:58.236 \rightarrow 00:26:00.618$  determine the splicing changes into

NOTE Confidence: 0.765729881111111

 $00:26:00.618 \rightarrow 00:26:03.480$  not only the marine model systems,

NOTE Confidence: 0.76572988111111

 $00{:}26{:}03.480 \dashrightarrow 00{:}26{:}06.620$  but also patient derived samples.

NOTE Confidence: 0.765729881111111

00:26:06.620 --> 00:26:08.804 I just want to skip quickly through

NOTE Confidence: 0.765729881111111

 $00:26:08.804 \longrightarrow 00:26:10.966$  this just so I can get here to

NOTE Confidence: 0.765729881111111

 $00{:}26{:}10.966 \dashrightarrow 00{:}26{:}12.947$  how are we going to target these

NOTE Confidence: 0.765729881111111

 $00{:}26{:}12{.}947 \dashrightarrow 00{:}26{:}14{.}809$  mutant splicing factor proteins.

NOTE Confidence: 0.76572988111111

 $00:26:14.810 \longrightarrow 00:26:15.626$  So similarly,

 $00:26:15.626 \longrightarrow 00:26:18.730$  we use the 8800 compound and we are

NOTE Confidence: 0.76572988111111

 $00{:}26{:}18.730 \dashrightarrow 00{:}26{:}21.128$  now finding that also these mutant

NOTE Confidence: 0.765729881111111

 $00:26:21.128 \rightarrow 00:26:24.229$  cells are very sensitive to this compound.

NOTE Confidence: 0.76572988111111

 $00:26:24.230 \longrightarrow 00:26:27.392$  We are also finding that these

NOTE Confidence: 0.765729881111111

 $00:26:27.392 \rightarrow 00:26:30.402$  mutations confer sensitivity to certain

NOTE Confidence: 0.76572988111111

 $00{:}26{:}30{.}402 \dashrightarrow 00{:}26{:}32{.}570$  chemotherapeutic agents. In this case.

NOTE Confidence: 0.765729881111111

 $00:26:32.570 \longrightarrow 00:26:34.546$  In particular, the case 700 E.

NOTE Confidence: 0.765729881111111

00:26:34.546 --> 00:26:35.548 As of Feb,

NOTE Confidence: 0.765729881111111

 $00:26:35.550 \longrightarrow 00:26:37.160$  one is more sensitive to

NOTE Confidence: 0.76572988111111

 $00:26:37.160 \longrightarrow 00:26:39.349$  gemcitabine than it is to five FU.

NOTE Confidence: 0.76572988111111

 $00:26:39.350 \rightarrow 00:26:41.516$  So this is important because these

NOTE Confidence: 0.76572988111111

 $00{:}26{:}41.516 \dashrightarrow 00{:}26{:}43.294$  mutation profiling can also help

NOTE Confidence: 0.765729881111111

 $00:26:43.294 \rightarrow 00:26:45.226$  to decide what would be the best.

NOTE Confidence: 0.765729881111111

 $00{:}26{:}45{.}230 \dashrightarrow 00{:}26{:}47{.}242$  Chemotherapeutic agent who assigned

NOTE Confidence: 0.765729881111111

 $00{:}26{:}47.242 \dashrightarrow 00{:}26{:}50.260$  to a particular patient and when

 $00:26:50.335 \longrightarrow 00:26:52.480$  we did combination studies on

NOTE Confidence: 0.76572988111111

 $00:26:52.480 \longrightarrow 00:26:55.535$  mixing gemcitabine with 8800 in

NOTE Confidence: 0.76572988111111

00:26:55.535 --> 00:26:57.979 mutant versus wildtype cells,

NOTE Confidence: 0.765729881111111

 $00:26:57.980 \rightarrow 00:27:00.804$  we can see that the mutant cells are

NOTE Confidence: 0.765729881111111

 $00{:}27{:}00{.}804 \dashrightarrow 00{:}27{:}02{.}593$  more sensitive to the combination

NOTE Confidence: 0.765729881111111

 $00{:}27{:}02{.}593 \dashrightarrow 00{:}27{:}05{.}555$  of jam and 8800 more so than the NOTE Confidence: 0.765729881111111

 $00{:}27{:}05{.}555 \dashrightarrow 00{:}27{:}08{.}049$  wild type cells suggesting that this

NOTE Confidence: 0.76572988111111

 $00:27:08.049 \rightarrow 00:27:10.339$  combination of therapy could be

NOTE Confidence: 0.76572988111111

00:27:10.339 --> 00:27:12.634 important to treating the patients

NOTE Confidence: 0.765729881111111

 $00:27:12.634 \rightarrow 00:27:15.350$  that have these K 700 E mutation.

NOTE Confidence: 0.76572988111111

 $00:27:15.350 \longrightarrow 00:27:16.622$  That's up 31,

NOTE Confidence: 0.76572988111111

 $00:27:16.622 \longrightarrow 00:27:19.590$  so I just want to finalize by

NOTE Confidence: 0.76572988111111

00:27:19.697 --> 00:27:21.674 saying that I'm currently based

NOTE Confidence: 0.76572988111111

 $00{:}27{:}21.674 \dashrightarrow 00{:}27{:}23.750$  on our findings on Mutant P.

NOTE Confidence: 0.765729881111111

 $00{:}27{:}23.750 \dashrightarrow 00{:}27{:}25.170$  53 and mutant SFB.

NOTE Confidence: 0.765729881111111

00:27:25.170 --> 00:27:28.430 One and RBM 10 laws as the drivers,

- NOTE Confidence: 0.765729881111111
- $00:27:28.430 \longrightarrow 00:27:29.615$  as pancreatic cancer.
- NOTE Confidence: 0.765729881111111
- $00:27:29.615 \longrightarrow 00:27:31.985$  All of these mutations leading to
- NOTE Confidence: 0.765729881111111
- $00:27:31.985 \rightarrow 00:27:33.948$  changes in alternative splicing.
- NOTE Confidence: 0.765729881111111
- $00:27:33.950 \rightarrow 00:27:37.359$  We're hoping to also bring into the
- NOTE Confidence: 0.765729881111111
- $00{:}27{:}37{.}359 \dashrightarrow 00{:}27{:}39{.}303$  trial patients eligible patients
- NOTE Confidence: 0.765729881111111
- $00{:}27{:}39{.}303 \dashrightarrow 00{:}27{:}42{.}471$  that are case 100 mutant or have RBM
- NOTE Confidence: 0.76572988111111
- $00:27:42.471 \longrightarrow 00:27:45.348$  10 lost to be eligible for this.
- NOTE Confidence: 0.765729881111111
- $00:27:45.350 \rightarrow 00:27:47.345$  Glycine anti silicene therapy that
- NOTE Confidence: 0.76572988111111
- 00:27:47.345 --> 00:27:49.340 we wanna lounge in combination
- NOTE Confidence: 0.765729881111111
- $00{:}27{:}49{.}407 \dashrightarrow 00{:}27{:}51{.}252$  with Gemini and Gemini 8800 and
- NOTE Confidence: 0.76572988111111
- $00{:}27{:}51{.}252 \dashrightarrow 00{:}27{:}53{.}220$  so with that I wanna wrap up by
- NOTE Confidence: 0.875053478
- $00{:}27{:}53{.}283 \dashrightarrow 00{:}27{:}55{.}461$  saying thank you to every one here
- NOTE Confidence: 0.875053478
- $00{:}27{:}55{.}461 \dashrightarrow 00{:}27{:}57{.}766$  for your attendance today to all the NOTE Confidence: 0.875053478
- $00:27:57.766 \rightarrow 00:27:59.614$  people in my lab who are leading
- NOTE Confidence: 0.875053478
- $00{:}27{:}59.620 \dashrightarrow 00{:}28{:}02.068$  this effort to all our collaborators
- NOTE Confidence: 0.875053478

 $00:28:02.068 \rightarrow 00:28:05.039$  and also to our funding sources.

NOTE Confidence: 0.875053478

00:28:05.040 --> 00:28:06.732 Thank you very much and I'll

NOTE Confidence: 0.875053478

 $00:28:06.732 \longrightarrow 00:28:08.120$  take any questions. Thank you.

NOTE Confidence: 0.810624796

00:28:09.060 -> 00:28:10.400 Thank you so much Teresa,

NOTE Confidence: 0.810624796

 $00:28:10.400 \longrightarrow 00:28:12.520$  that was really fascinating

NOTE Confidence: 0.810624796

 $00:28:12.520 \longrightarrow 00:28:16.160$  work at great, excellent stuff.

NOTE Confidence: 0.810624796

00:28:16.160 --> 00:28:19.843 If people have questions for Louisa,

NOTE Confidence: 0.810624796

 $00:28:19.843 \longrightarrow 00:28:23.014$  please put them in the chat and

NOTE Confidence: 0.810624796

 $00{:}28{:}23.014 \dashrightarrow 00{:}28{:}25.930$  I can read them to her and she

NOTE Confidence: 0.810624796

 $00:28:25.930 \longrightarrow 00:28:28.340$  can go ahead and answer them.

NOTE Confidence: 0.810624796

 $00{:}28{:}28{.}340 \dashrightarrow 00{:}28{:}30{.}510$  I had one quick question.

NOTE Confidence: 0.810624796

00:28:30.510 --> 00:28:32.970 While people are formulating their thoughts,

NOTE Confidence: 0.810624796

 $00:28:32.970 \longrightarrow 00:28:36.708$  which is it is intriguing that

NOTE Confidence: 0.810624796

00:28:36.710 -> 00:28:38.348 the mutations and the and effects,

NOTE Confidence: 0.810624796

 $00{:}28{:}38{.}350 \dashrightarrow 00{:}28{:}43{.}200$  and indeed the the the.

NOTE Confidence: 0.810624796

 $00:28:43.200 \longrightarrow 00:28:46.084$  8800 are all focusing on you two.

- NOTE Confidence: 0.810624796
- 00:28:46.090 -> 00:28:50.790 Do you have some? He's out.

 $00:28:50.790 \longrightarrow 00:28:51.870$  It may be migraines,

NOTE Confidence: 0.810624796

 $00:28:51.870 \rightarrow 00:28:54.010$  but what does that mean, mechanistically?

NOTE Confidence: 0.884566718333333

00:28:55.130 - 00:28:57.490 Yeah, thank you Mark.

NOTE Confidence: 0.884566718333333

 $00:28:57.490 \rightarrow 00:29:00.320$  So basically the compound targets

NOTE Confidence: 0.884566718333333

 $00{:}29{:}00{.}320 \dashrightarrow 00{:}29{:}03{.}226$  mutant SF 3B1 and so it's the

NOTE Confidence: 0.884566718333333

 $00:29:03.226 \longrightarrow 00:29:05.970$  tumors have mutant SF 3B1.

NOTE Confidence: 0.884566718333333

 $00:29:05.970 \rightarrow 00:29:08.168$  They are more sensitive to this compound,

NOTE Confidence: 0.884566718333333

 $00:29:08.170 \longrightarrow 00:29:10.144$  so that's the case for S3 one.

NOTE Confidence: 0.884566718333333

 $00:29:10.150 \longrightarrow 00:29:12.774$  But we also know that the if if

NOTE Confidence: 0.884566718333333

00:29:12.774 --> 00:29:14.890 tumors highly depend on splicing.

NOTE Confidence: 0.884566718333333

 $00{:}29{:}14.890 \dashrightarrow 00{:}29{:}17.992$  There there are more sensitive to

NOTE Confidence: 0.884566718333333

 $00:29:17.992 \longrightarrow 00:29:20.335$  this compound because they cannot

NOTE Confidence: 0.884566718333333

 $00{:}29{:}20{.}335 \dashrightarrow 00{:}29{:}22{.}945$  tolerate a double perturbation of the

NOTE Confidence: 0.884566718333333

 $00{:}29{:}22{.}945 \dashrightarrow 00{:}29{:}25{.}099$  splicing changes and the splicing.

 $00:29:25.100 \rightarrow 00:29:29.293$  Machinery and so that's how we are

NOTE Confidence: 0.884566718333333

00:29:29.293 --> 00:29:31.928 attributing the sensitivity of of

NOTE Confidence: 0.884566718333333

00:29:31.928 --> 00:29:35.363 mutant P 53 and mutant RBM 10 to 8800,

NOTE Confidence: 0.884566718333333

 $00:29:35.363 \rightarrow 00:29:38.814$  and I think more dissection of the

NOTE Confidence: 0.884566718333333

 $00:29:38.814 \rightarrow 00:29:42.038$  mechanism of the drug within you.

NOTE Confidence: 0.884566718333333

 $00{:}29{:}42.040 \dashrightarrow 00{:}29{:}45.008$  Know RBM 10 and P53 can further elucidate

NOTE Confidence: 0.884566718333333

 $00:29:45.008 \rightarrow 00:29:48.486$  why are they so sensitive to this compound,

NOTE Confidence: 0.884566718333333

 $00:29:48.490 \longrightarrow 00:29:49.722$  at least for P53.

NOTE Confidence: 0.884566718333333

 $00{:}29{:}49{.}722 \dashrightarrow 00{:}29{:}51{.}570$  We know that in certain cases

NOTE Confidence: 0.884566718333333

00:29:51.637 --> 00:29:53.209 it reverses the effects.

NOTE Confidence: 0.884566718333333

 $00{:}29{:}53{.}210$  -->  $00{:}29{:}55{.}590$  The splicing changes that mutant P 53.

NOTE Confidence: 0.884566718333333

 $00:29:55.590 \rightarrow 00:29:56.410$  Is promoting.

NOTE Confidence: 0.786254627222222

 $00{:}29{:}58{.}590 \dashrightarrow 00{:}30{:}00{.}594$  Make makes sense and the other

NOTE Confidence: 0.786254627222222

 $00:30:00.594 \rightarrow 00:30:02.896$  question I had was that we're going

NOTE Confidence: 0.786254627222222

 $00:30:02.896 \longrightarrow 00:30:06.090$  back to the gap 17 story. Do you see?

NOTE Confidence: 0.786254627222222

 $00:30:06.090 \rightarrow 00:30:09.196$  In other circumstances the if you look

- NOTE Confidence: 0.786254627222222
- $00:30:09.196 \longrightarrow 00:30:12.040$  through other cells and and indeed
- NOTE Confidence: 0.786254627222222
- $00{:}30{:}12.040 \dashrightarrow 00{:}30{:}14.906$  tumors that aren't don't have the
- NOTE Confidence: 0.786254627222222
- $00{:}30{:}14.906 \dashrightarrow 00{:}30{:}17.630$  the gain of function P53 mutations.
- NOTE Confidence: 0.786254627222222
- $00:30:17.630 \longrightarrow 00:30:21.678$  Do you see the the gap 17 with
- NOTE Confidence: 0.786254627222222
- $00:30:21.678 \dashrightarrow 00:30:24.438$  the policy Exxon in other places?
- NOTE Confidence: 0.81168588
- $00:30:25.030 \longrightarrow 00:30:26.788$  Yeah, so that's a good question.
- NOTE Confidence: 0.81168588
- $00:30:26.790 \longrightarrow 00:30:27.870$  So for example.
- NOTE Confidence: 0.81168588
- $00:30:27.870 \dashrightarrow 00:30:29.670$  We've looked into other cancers
- NOTE Confidence: 0.81168588
- $00:30:29.670 \longrightarrow 00:30:31.660$  that are not key, rest driven,
- NOTE Confidence: 0.81168588
- 00:30:31.660 --> 00:30:34.172 but have this mutant form of P53,
- NOTE Confidence: 0.81168588
- $00:30:34.172 \longrightarrow 00:30:36.824$  and we see that indeed the
- NOTE Confidence: 0.81168588
- $00:30:36.824 \rightarrow 00:30:39.070$  splicing changing gap 17 occurs.
- NOTE Confidence: 0.81168588
- $00{:}30{:}39{.}070 \dashrightarrow 00{:}30{:}42{.}198$  Now we have also seen some other tumors
- NOTE Confidence: 0.81168588
- 00:30:42.198 --> 00:30:44.865 where mutant P 53 is not present and
- NOTE Confidence: 0.81168588
- 00:30:44.865 00:30:47.350 we still see the splicing change,
- NOTE Confidence: 0.81168588

 $00:30:47.350 \dashrightarrow 00:30:49.954$  and we think that this is attributed

NOTE Confidence: 0.81168588

 $00:30:49.954 \rightarrow 00:30:52.175$  to the overexpression of a splicing

NOTE Confidence: 0.81168588

 $00{:}30{:}52{.}175 \dashrightarrow 00{:}30{:}54{.}170$  factor called H&R AMPK that today

NOTE Confidence: 0.81168588

00:30:54.170 --> 00:30:56.570 I didn't have time to go into,

NOTE Confidence: 0.81168588

 $00{:}30{:}56{.}570 \dashrightarrow 00{:}30{:}58{.}628$  but we think that this splicing.

NOTE Confidence: 0.81168588

 $00:30:58.630 \rightarrow 00:31:03.260$  Regulator also promotes the policy.

NOTE Confidence: 0.81168588

00:31:03.260 --> 00:31:06.113 The the policy acts on inclusion in M RNA,

NOTE Confidence: 0.81168588

 $00:31:06.120 \longrightarrow 00:31:08.171$  so we think that there is not

NOTE Confidence: 0.81168588

 $00{:}31{:}08{.}171 \dashrightarrow 00{:}31{:}10{.}376$  a single pathway to to promote.

NOTE Confidence: 0.81168588

 $00:31:10.376 \dashrightarrow 00:31:13.470$  The policy acts on retention in gaps.

NOTE Confidence: 0.735722408789474

 $00{:}31{:}15{.}000 \dashrightarrow 00{:}31{:}17{.}653$  This is fascinating and I have a

NOTE Confidence: 0.735722408789474

 $00{:}31{:}17.653 \dashrightarrow 00{:}31{:}20.239$  question in the chat from from

NOTE Confidence: 0.735722408789474

00:31:20.239 --> 00:31:22.975 Timothy Robinson who says great talk.

NOTE Confidence: 0.735722408789474

 $00{:}31{:}22.980 \dashrightarrow 00{:}31{:}25.528$  I agree with the way you described

NOTE Confidence: 0.735722408789474

 $00:31:25.528 \rightarrow 00:31:27.433$  using mutually exclusive analysis to

NOTE Confidence: 0.735722408789474

 $00{:}31{:}27{.}433 \dashrightarrow 00{:}31{:}29{.}659$  find events within the same pathway.

- NOTE Confidence: 0.735722408789474
- 00:31:29.660 --> 00:31:31.568 Did you look at Gap 17?
- NOTE Confidence: 0.735722408789474
- 00:31:31.570 --> 00:31:34.625 Aberrant splicing based on mRNA
- NOTE Confidence: 0.735722408789474
- 00:31:34.625 --> 00:31:36.828 directly to identify other drivers?
- NOTE Confidence: 0.880845552222222
- 00:31:38.870 --> 00:31:40.118 So I'm not sure if I'm
- NOTE Confidence: 0.880845552222222
- $00{:}31{:}40{.}118 \dashrightarrow 00{:}31{:}40{.}742$  understanding the question.
- NOTE Confidence: 0.880845552222222
- 00:31:40.750 --> 00:31:43.943 If I if we looked into into
- NOTE Confidence: 0.880845552222222
- $00:31:43.943 \longrightarrow 00:31:46.566$  other pathways that are not
- NOTE Confidence: 0.880845552222222
- 00:31:46.566 00:31:49.014 linked to to the cares pathway.
- NOTE Confidence: 0.7772512666666667
- 00:31:49.110 --> 00:31:50.340 I think the question is
- NOTE Confidence: 0.7772512666666667
- 00:31:50.340 --> 00:31:51.324 actually did you look?
- NOTE Confidence: 0.7772512666666667
- $00:31:51.330 \longrightarrow 00:31:52.675$  Did you look at aberrant
- NOTE Confidence: 0.7772512666666667
- $00{:}31{:}52.675 \dashrightarrow 00{:}31{:}54.380$  splicing based on M RNA to
- NOTE Confidence: 0.7772512666666667
- $00:31:54.380 \longrightarrow 00:31:55.588$  identify other drivers that
- NOTE Confidence: 0.7772512666666667
- $00{:}31{:}55{.}588 \dashrightarrow 00{:}31{:}57{.}330$  might be other than gap 17?
- NOTE Confidence: 0.7772512666666667
- $00:31:57.330 \longrightarrow 00:31:57.939$  I think that's
- NOTE Confidence: 0.754027668045454

 $00:31:58.660 \rightarrow 00:32:01.012$  yeah. So all the splicing changes

NOTE Confidence: 0.754027668045454

 $00:32:01.012 \longrightarrow 00:32:03.910$  that we identified are based on mRNA

NOTE Confidence: 0.754027668045454

 $00:32:03.910 \rightarrow 00:32:06.010$  sequencing and based on splicing

NOTE Confidence: 0.754027668045454

00:32:06.010 - 00:32:08.776 analysis that we conduct. But if I.

NOTE Confidence: 0.754027668045454

 $00{:}32{:}08{.}776 \dashrightarrow 00{:}32{:}12{.}111$  But I can also mention that the gaps are

NOTE Confidence: 0.754027668045454

 $00{:}32{:}12{.}111 \dashrightarrow 00{:}32{:}14{.}738$  only 5% of the events that mutant be 50,

NOTE Confidence: 0.754027668045454

 $00:32:14.740 \longrightarrow 00:32:17.169$  three, 5% of the event is splicing

NOTE Confidence: 0.754027668045454

 $00:32:17.169 \rightarrow 00:32:19.520$  events that mutant P 53 is triggering.

NOTE Confidence: 0.754027668045454

 $00{:}32{:}19{.}520 \dashrightarrow 00{:}32{:}22{.}296$  So there are other M RNA's that affect

NOTE Confidence: 0.754027668045454

 $00:32:22.296 \dashrightarrow 00:32:24.961$  other pathways that are being impacted by

NOTE Confidence: 0.754027668045454

 $00:32:24.961 \rightarrow 00:32:27.334$  the aberrant splicing by mutant P. 53.

NOTE Confidence: 0.754027668045454

 $00{:}32{:}27{.}334 \dashrightarrow 00{:}32{:}29{.}800$  So we just went with the gaps to start

NOTE Confidence: 0.754027668045454

 $00:32:29.873 \dashrightarrow 00:32:32.253$  with because of course of the relevance

NOTE Confidence: 0.754027668045454

 $00{:}32{:}32{.}253 \dashrightarrow 00{:}32{:}34.777$  and the path and the Keras pathway.

NOTE Confidence: 0.754027668045454

 $00{:}32{:}34.780 \dashrightarrow 00{:}32{:}37.130$  But we are there is a student in the lab

NOTE Confidence: 0.754027668045454

 $00:32:37.192 \longrightarrow 00:32:39.307$  who's actually trying to understand.

- NOTE Confidence: 0.754027668045454
- $00:32:39.310 \longrightarrow 00:32:39.625$  What?
- NOTE Confidence: 0.754027668045454
- $00:32:39.625 \rightarrow 00:32:42.145$  What is the role of the other splicing
- NOTE Confidence: 0.754027668045454
- 00:32:42.145 --> 00:32:44.640 changes in other M RNA's that are not gaps?
- NOTE Confidence: 0.806719478
- 00:32:46.690 --> 00:32:48.850 And presumably, in that context,
- NOTE Confidence: 0.806719478
- 00:32:48.850 --> 00:32:50.368 I mean, it's kind of interesting
- NOTE Confidence: 0.806719478
- $00{:}32{:}50{.}368 \dashrightarrow 00{:}32{:}52{.}674$  that the gap 17 effect is so
- NOTE Confidence: 0.806719478
- $00:32:52.674 \rightarrow 00:32:54.990$  kind of singular in a sense,
- NOTE Confidence: 0.806719478
- $00:32:54.990 \longrightarrow 00:32:56.740$  and you presumably in the other cases
- NOTE Confidence: 0.806719478
- $00{:}32{:}56{.}740 \dashrightarrow 00{:}32{:}58{.}551$  it's really going to be a combination
- NOTE Confidence: 0.806719478
- $00:32:58.551 \longrightarrow 00:33:00.075$  that's going to be the constellation
- NOTE Confidence: 0.806719478
- $00:33:00.126 \longrightarrow 00:33:01.488$  of those changes that are key,
- NOTE Confidence: 0.806719478
- $00:33:01.490 \dashrightarrow 00:33:02.882$  which is going to be interesting
- NOTE Confidence: 0.806719478
- $00:33:02.882 \longrightarrow 00:33:04.000$  but tough to tease out
- NOTE Confidence: 0.880829711666667
- $00{:}33{:}04{.}110 \dashrightarrow 00{:}33{:}06{.}360$  exactly. So, as I mentioned before,
- NOTE Confidence: 0.880829711666667
- $00{:}33{:}06{.}360 \dashrightarrow 00{:}33{:}09{.}909$  we are seeing that 32 gaps encoded
- NOTE Confidence: 0.880829711666667

 $00:33:09.909 \rightarrow 00:33:13.459$  by the genome of of 120 dots that

NOTE Confidence: 0.880829711666667

 $00:33:13.459 \rightarrow 00:33:15.774$  are encoded are being differentially

NOTE Confidence: 0.880829711666667

 $00:33:15.774 \longrightarrow 00:33:17.178$  spliced, we manipulated.

NOTE Confidence: 0.880829711666667

00:33:17.178 --> 00:33:19.992 One, but if you imagine manipulating

NOTE Confidence: 0.880829711666667

 $00:33:19.992 \longrightarrow 00:33:22.265$  several of them and forcing

NOTE Confidence: 0.880829711666667

 $00:33:22.265 \longrightarrow 00:33:24.360$  policy axons to be excluded,

NOTE Confidence: 0.8808297116666667

 $00:33:24.360 \rightarrow 00:33:26.352$  the the effect might be synergistic

NOTE Confidence: 0.880829711666667

 $00:33:26.352 \longrightarrow 00:33:28.915$  in terms of the the cell

NOTE Confidence: 0.880829711666667

 $00{:}33{:}28{.}915$  -->  $00{:}33{:}30{.}865$  proliferation and the tumor growth.

NOTE Confidence: 0.7890346

 $00:33:33.000 \rightarrow 00:33:35.958$  Sure. Any other questions in the chat?

NOTE Confidence: 0.725700857857143

 $00:33:38.690 \longrightarrow 00:33:39.901$  So we don't seem to have at

NOTE Confidence: 0.725700857857143

00:33:39.901 - > 00:33:41.190 the moment of so that we could,

NOTE Confidence: 0.725700857857143

 $00:33:41.190 \rightarrow 00:33:43.990$  and we we we should probably move on.

NOTE Confidence: 0.725700857857143

00:33:43.990 - 00:33:45.892 So thank you very much, Lisa.

NOTE Confidence: 0.725700857857143

 $00{:}33{:}45{.}892 \dashrightarrow 00{:}33{:}47{.}584$  That was a fascinating stuff with

NOTE Confidence: 0.725700857857143

 $00:33:47.584 \longrightarrow 00:33:49.370$  the enormous about everyone.

- NOTE Confidence: 0.725700857857143
- 00:33:49.370 --> 00:33:52.078 And to think about it. Thank you.
- NOTE Confidence: 0.725700857857143
- $00{:}33{:}52.078 \dashrightarrow 00{:}33{:}57.345$  So, so let's move on for the second
- NOTE Confidence: 0.725700857857143
- $00{:}33{:}57{.}345 \dashrightarrow 00{:}34{:}01{.}360$  half to Doctor Rosa Vinod Zikula.
- NOTE Confidence: 0.725700857857143
- 00:34:01.360 --> 00:34:03.614 So Doctor Zickler is an assistant professor
- NOTE Confidence: 0.725700857857143
- $00:34:03.614 \dashrightarrow 00:34:05.679$  of medicine and digestive diseases.
- NOTE Confidence: 0.725700857857143
- $00:34:05.680 \longrightarrow 00:34:08.224$  She received her PhD from the
- NOTE Confidence: 0.725700857857143
- 00:34:08.224 --> 00:34:10.760 university app Autonomo de Barcelona.
- NOTE Confidence: 0.725700857857143
- 00:34:10.760 --> 00:34:12.535 I apologize for my pronunciation
- NOTE Confidence: 0.725700857857143
- $00{:}34{:}12.535 \dashrightarrow 00{:}34{:}14.310$  and oncology and her postdoctoral
- NOTE Confidence: 0.725700857857143
- $00:34:14.366 \rightarrow 00:34:16.364$  training at the Institute of Cancer
- NOTE Confidence: 0.725700857857143
- $00{:}34{:}16{.}364 \dashrightarrow 00{:}34{:}18{.}070$  Research at the University of
- NOTE Confidence: 0.725700857857143
- $00{:}34{:}18.070 \dashrightarrow 00{:}34{:}19.640$ Illinois and at Yale University.
- NOTE Confidence: 0.725700857857143
- $00:34:19.640 \dashrightarrow 00:34:22.056$  Dr Zickler's long term goal is to decipher.
- NOTE Confidence: 0.725700857857143
- $00{:}34{:}22.060 \dashrightarrow 00{:}34{:}24.172$  Known genetic alterations that
- NOTE Confidence: 0.725700857857143
- $00{:}34{:}24.172 \dashrightarrow 00{:}34{:}26.284$  predispose to colorectal cancer
- NOTE Confidence: 0.725700857857143

 $00:34:26.284 \rightarrow 00:34:28.758$  development and her research focus

NOTE Confidence: 0.725700857857143

 $00:34:28.758 \longrightarrow 00:34:31.440$  is on understanding molecular and the

NOTE Confidence: 0.725700857857143

00:34:31.440 --> 00:34:33.545 molecular characterization of sporadic NOTE Confidence: 0.725700857857143

 $00:34:33.545 \rightarrow 00:34:35.657$  and hereditary colorectal cancer

NOTE Confidence: 0.725700857857143

 $00{:}34{:}35{.}657 \dashrightarrow 00{:}34{:}38{.}224$  with an interest in understanding

NOTE Confidence: 0.725700857857143

00:34:38.224 --> 00:34:40.172 the biological differences among

NOTE Confidence: 0.725700857857143

 $00:34:40.172 \longrightarrow 00:34:42.230$  racial groups to develop her

NOTE Confidence: 0.725700857857143

 $00{:}34{:}42{.}230 \dashrightarrow 00{:}34{:}43{.}310$  translational research doctors.

NOTE Confidence: 0.725700857857143

00:34:43.310 --> 00:34:47.339 Zigler is a key player in several

NOTE Confidence: 0.725700857857143

 $00:34:47.339 \dashrightarrow 00:34:49.135$  repositories and consortia that

NOTE Confidence: 0.725700857857143

 $00{:}34{:}49{.}135 \dashrightarrow 00{:}34{:}50{.}931$  recruit cancer patients and

NOTE Confidence: 0.725700857857143

 $00:34:50.931 \rightarrow 00:34:52.939$  then collecting biospecimens.

NOTE Confidence: 0.725700857857143

 $00{:}34{:}52{.}940 \dashrightarrow 00{:}34{:}55{.}406$  And and clinical data and Doctor

NOTE Confidence: 0.725700857857143

 $00{:}34{:}55{.}406 \dashrightarrow 00{:}34{:}58{.}608$ Nikola will will tell us about defining

NOTE Confidence: 0.725700857857143

 $00:34:58.608 \rightarrow 00:35:01.078$  new pathways in colorectal tumors

NOTE Confidence: 0.725700857857143

 $00:35:01.078 \rightarrow 00:35:03.520$  with mismatch repair deficiency.

- NOTE Confidence: 0.725700857857143
- $00:35:03.520 \rightarrow 00:35:05.000$  So thanks so much Rosa for doing this.
- NOTE Confidence: 0.725700857857143
- 00:35:05.000 --> 00:35:06.540 I really look forward to your talk.
- NOTE Confidence: 0.914238268
- $00:35:07.590 \longrightarrow 00:35:09.680$  Thank you, let me share.
- NOTE Confidence: 0.9334385475
- $00:35:14.750 \longrightarrow 00:35:17.610$  Can you see properly?
- NOTE Confidence: 0.9334385475
- 00:35:17.610 --> 00:35:19.890 OK, so thank you so much for giving
- NOTE Confidence: 0.9334385475
- $00{:}35{:}19{.}890 \dashrightarrow 00{:}35{:}22{.}491$  me the priority to show you all our
- NOTE Confidence: 0.9334385475
- $00:35:22.491 \longrightarrow 00:35:25.050$  most recent data on the topic of
- NOTE Confidence: 0.9334385475
- $00:35:25.050 \rightarrow 00:35:26.556$  mismatch repair, deficient tools.
- NOTE Confidence: 0.9334385475
- $00:35:26.556 \dashrightarrow 00:35:29.700$  So the outline of the talk is going to.
- NOTE Confidence: 0.9334385475
- 00:35:29.700 --> 00:35:31.748 I'm going to explain you give you an
- NOTE Confidence: 0.9334385475
- $00:35:31.748 \rightarrow 00:35:34.328$  overview of the mismatch repair and the
- NOTE Confidence: 0.9334385475
- $00:35:34.328 \longrightarrow 00:35:35.940$  phenomena of microsatellite instability.
- NOTE Confidence: 0.9334385475
- $00:35:35.940 \longrightarrow 00:35:38.432$  And then I will explain you the
- NOTE Confidence: 0.9334385475
- $00{:}35{:}38{.}432 \dashrightarrow 00{:}35{:}40{.}318$  clinical phenotypes and challenges in
- NOTE Confidence: 0.9334385475
- $00{:}35{:}40{.}318 \dashrightarrow 00{:}35{:}42{.}943$  the molecular that I diagnosis of the
- NOTE Confidence: 0.9334385475

 $00:35:42.943 \longrightarrow 00:35:45.399$  tumors that have mismatched efficient.

NOTE Confidence: 0.9334385475

 $00{:}35{:}45{.}400 \dashrightarrow 00{:}35{:}48{.}627$  Then I will explain you the association.

NOTE Confidence: 0.9334385475

 $00{:}35{:}48.630 \dashrightarrow 00{:}35{:}50.870$  That we are describing between

NOTE Confidence: 0.9334385475

 $00{:}35{:}50.870 \dashrightarrow 00{:}35{:}53.695$  deficiency of RAQUE and DNA helicases

NOTE Confidence: 0.9334385475

00:35:53.695 - 00:35:56.205 in Lynch like syndrome cases.

NOTE Confidence: 0.9334385475

 $00{:}35{:}56{.}210 \dashrightarrow 00{:}35{:}58{.}744$  And then I will show our most

NOTE Confidence: 0.9334385475

 $00{:}35{:}58{.}750 \dashrightarrow 00{:}36{:}00{.}362$  recent publication that describes

NOTE Confidence: 0.9334385475

 $00:36:00.362 \dashrightarrow 00:36:02.377$  the identification of tumors with

NOTE Confidence: 0.9334385475

 $00{:}36{:}02{.}377 \dashrightarrow 00{:}36{:}04{.}871$ a high likelihood development and

NOTE Confidence: 0.9334385475

 $00:36:04.871 \rightarrow 00:36:06.903$  immune response through mutational

NOTE Confidence: 0.9334385475

 $00:36:06.903 \longrightarrow 00:36:07.919$  signature profiling.

NOTE Confidence: 0.729921572

 $00:36:10.100 \longrightarrow 00:36:12.476$  So here in the left you can see that

NOTE Confidence: 0.729921572

 $00:36:12.476 \rightarrow 00:36:15.205$  it's a cartoon that shows the the mosque

NOTE Confidence: 0.729921572

 $00:36:15.205 \rightarrow 00:36:17.897$  important for the main proteins that are NOTE Confidence: 0.729921572

 $00:36:17.897 \rightarrow 00:36:20.297$  involved in the mismatch repair system.

NOTE Confidence: 0.729921572

 $00:36:20.300 \rightarrow 00:36:23.037$  The mismatch repair system is the inner

 $00{:}36{:}23{.}037 \dashrightarrow 00{:}36{:}25{.}932$  repair system that identifies mismatches like

NOTE Confidence: 0.729921572

 $00:36:25.932 \rightarrow 00:36:29.334$  single base base or like larger mismatches.

NOTE Confidence: 0.729921572

 $00:36:29.340 \longrightarrow 00:36:31.000$  And there's two main complexes,

NOTE Confidence: 0.729921572

 $00{:}36{:}31{.}000 \dashrightarrow 00{:}36{:}34{.}132$  the mute test that it's formed by message 6

NOTE Confidence: 0.729921572

 $00:36:34.132 \rightarrow 00:36:37.517$  and Message 2 and Message 3 and a message 2.

NOTE Confidence: 0.729921572

 $00{:}36{:}37{.}520 \dashrightarrow 00{:}36{:}38{.}990$  So these proteins are the

NOTE Confidence: 0.729921572

 $00:36:38.990 \longrightarrow 00:36:40.460$  first ones to recognize them.

NOTE Confidence: 0.729921572

 $00:36:40.460 \rightarrow 00:36:43.930$  As my tools and then the mute L complexes

NOTE Confidence: 0.729921572

 $00{:}36{:}43{.}930 \dashrightarrow 00{:}36{:}47{.}570$  recruited to help fix the the mismatches

NOTE Confidence: 0.729921572

 $00:36:47.570 \dashrightarrow 00:36:51.433$  and mutl is formed by PMS two and MLH 1.

NOTE Confidence: 0.729921572

 $00:36:51.440 \longrightarrow 00:36:53.792$  So in the genome there are these

NOTE Confidence: 0.729921572

 $00{:}36{:}53.792 \dashrightarrow 00{:}36{:}55.775$  sequences that are called microsatellites

NOTE Confidence: 0.729921572

 $00{:}36{:}55{.}775 \dashrightarrow 00{:}36{:}58{.}499$  that are prone to acquire alterations

NOTE Confidence: 0.729921572

 $00{:}36{:}58{.}499 \dashrightarrow 00{:}37{:}01{.}344$  when any of the proteins of the

NOTE Confidence: 0.729921572

 $00{:}37{:}01{.}344 \dashrightarrow 00{:}37{:}02{.}836$  mismatch repair not working.

 $00{:}37{:}02{.}840 \dashrightarrow 00{:}37{:}06{.}520$  So here you can see here you can

NOTE Confidence: 0.729921572

 $00{:}37{:}06{.}520 \dashrightarrow 00{:}37{:}08{.}838$  see sorry this is on the way.

NOTE Confidence: 0.729921572

 $00:37:08.840 \dashrightarrow 00:37:11.054$  Here you can see a microsatellite

NOTE Confidence: 0.729921572

 $00:37:11.054 \rightarrow 00:37:12.963$  microsatellites are short and repetitive

NOTE Confidence: 0.729921572

 $00:37:12.963 \dashrightarrow 00:37:14.833$  sequences present in coding and

NOTE Confidence: 0.729921572

 $00{:}37{:}14.833 \dashrightarrow 00{:}37{:}17.040$  non coding regions of the genome.

NOTE Confidence: 0.729921572

 $00:37:17.040 \longrightarrow 00:37:20.260$  And when the any of them is not

NOTE Confidence: 0.729921572

 $00:37:20.260 \longrightarrow 00:37:21.640$  working this Microsoft.

NOTE Confidence: 0.729921572

 $00:37:21.640 \longrightarrow 00:37:24.260$  That's accumulate deletions or insertions.

NOTE Confidence: 0.729921572

 $00{:}37{:}24.260 \dashrightarrow 00{:}37{:}27.074$  So when the size of the microsatellite

NOTE Confidence: 0.729921572

 $00:37:27.074 \longrightarrow 00:37:29.208$  cannot be properly kept during

NOTE Confidence: 0.729921572

00:37:29.208 --> 00:37:32.151 replication of DNA in the cells,

NOTE Confidence: 0.729921572

 $00:37:32.151 \dashrightarrow 00:37:34.379$  the phenomenon of microsatellite

NOTE Confidence: 0.729921572

 $00:37:34.379 \longrightarrow 00:37:36.869$  instability isn't identified in tumors.

NOTE Confidence: 0.807376979090909

00:37:39.920 --> 00:37:41.732 So I MSI can be identified

NOTE Confidence: 0.807376979090909

 $00:37:41.732 \longrightarrow 00:37:43.520$  in a variety of tumors,

- NOTE Confidence: 0.807376979090909
- $00:37:43.520 \longrightarrow 00:37:45.734$  but as you can see here on the table
- NOTE Confidence: 0.807376979090909
- $00{:}37{:}45{.}734 \dashrightarrow 00{:}37{:}48{.}256$  and in the graph in the material tumors,
- NOTE Confidence: 0.807376979090909
- $00{:}37{:}48.260 \dashrightarrow 00{:}37{:}50.505$  colorectal and stomach are the
- NOTE Confidence: 0.807376979090909
- $00{:}37{:}50{.}505 \dashrightarrow 00{:}37{:}53{.}641$  tumors that have a higher incidence
- NOTE Confidence: 0.807376979090909
- $00:37:53.641 \rightarrow 00:37:56.050$  of microsatellite instability.
- NOTE Confidence: 0.807376979090909
- 00:37:56.050 --> 00:37:57.794 So, in colorectal tumors,
- NOTE Confidence: 0.807376979090909
- $00:37:57.794 \longrightarrow 00:38:00.715$  about 10% of a sporadic tumors have
- NOTE Confidence: 0.807376979090909
- $00:38:00.715 \rightarrow 00:38:02.760$  mismatch repair deficiency and these
- NOTE Confidence: 0.807376979090909
- $00{:}38{:}02{.}831 \dashrightarrow 00{:}38{:}05{.}327$  deficiencies due to CPG island promoter
- NOTE Confidence: 0.807376979090909
- $00:38:05.327 \rightarrow 00:38:07.849$  musculation of the gene mileage one,
- NOTE Confidence: 0.807376979090909
- $00:38:07.850 \longrightarrow 00:38:10.104$  which I show you that it's a.
- NOTE Confidence: 0.807376979090909
- $00:38:10.110 \longrightarrow 00:38:12.006$  It's one of the two proteins
- NOTE Confidence: 0.807376979090909
- $00:38:12.006 \rightarrow 00:38:13.870$  that form the metal complex,
- NOTE Confidence: 0.807376979090909
- $00{:}38{:}13.870 \dashrightarrow 00{:}38{:}17.109$  so when there's a promoter methylation,
- NOTE Confidence: 0.807376979090909
- $00{:}38{:}17.109 \dashrightarrow 00{:}38{:}19.104$  there's an addition of transcription
- NOTE Confidence: 0.807376979090909

 $00{:}38{:}19{.}104 \dashrightarrow 00{:}38{:}21{.}970$  of the gene and it and resulting in

NOTE Confidence: 0.807376979090909

 $00{:}38{:}21{.}970 \dashrightarrow 00{:}38{:}24{.}330$  the loss of expression of the protein.

NOTE Confidence: 0.807376979090909

 $00:38:24.330 \rightarrow 00:38:26.297$  So here you can see the difference.

NOTE Confidence: 0.807376979090909

 $00:38:26.300 \rightarrow 00:38:28.308$  Between normal expression by

NOTE Confidence: 0.807376979090909

 $00{:}38{:}28{.}308 \dashrightarrow 00{:}38{:}29{.}814$  immunohistochemistry and loss

NOTE Confidence: 0.807376979090909

 $00:38:29.814 \rightarrow 00:38:32.488$  of expression and a significant

NOTE Confidence: 0.807376979090909

 $00:38:32.488 \longrightarrow 00:38:34.525$  number of these tumors,

NOTE Confidence: 0.807376979090909

 $00:38:34.525 \rightarrow 00:38:36.715$  they also present this hot spot

NOTE Confidence: 0.807376979090909

 $00{:}38{:}36{.}715 \dashrightarrow 00{:}38{:}38{.}879$  mutation in the Bureau of Gene.

NOTE Confidence: 0.807376979090909

 $00:38:38.880 \rightarrow 00:38:41.568$  Here you have the mutation and these

NOTE Confidence: 0.807376979090909

 $00{:}38{:}41{.}568 \dashrightarrow 00{:}38{:}44{.}168$  two are molecular events are used

NOTE Confidence: 0.807376979090909

 $00{:}38{:}44{.}168 \dashrightarrow 00{:}38{:}46{.}940$  to differentiate and tumors that

NOTE Confidence: 0.807376979090909

 $00:38:46.940 \rightarrow 00:38:49.848$  develop through a sporadic events.

NOTE Confidence: 0.807376979090909

 $00:38:49.848 \dashrightarrow 00:38:52.416$  Then the tumors that develop MSI

NOTE Confidence: 0.807376979090909

 $00:38:52.416 \longrightarrow 00:38:55.444$  but they are developing in the

NOTE Confidence: 0.807376979090909

 $00:38:55.444 \rightarrow 00:38:57.660$  setting of hereditary disease.

 $00:38:57.660 \rightarrow 00:39:02.259$  So Vince Syndrome is the the tumor.

NOTE Confidence: 0.807376979090909

 $00:39:02.260 \longrightarrow 00:39:03.409$  It's cancer syndrome.

NOTE Confidence: 0.807376979090909

 $00:39:03.409 \rightarrow 00:39:05.707$  There is due to germline mutations

NOTE Confidence: 0.807376979090909

00:39:05.707 - 00:39:07.919 in this mismatch repair genes.

NOTE Confidence: 0.807376979090909

 $00{:}39{:}07{.}920 \dashrightarrow 00{:}39{:}09{.}540$  It's actually the most common

NOTE Confidence: 0.807376979090909

 $00:39:09.540 \rightarrow 00:39:11.680$  cancer syndrome of all it's present.

NOTE Confidence: 0.807376979090909

00:39:11.680 - 00:39:14.188 It's estimated that one in 270 people

NOTE Confidence: 0.807376979090909

00:39:14.188 --> 00:39:16.860 in the US carry one of the mutation

NOTE Confidence: 0.807376979090909

 $00{:}39{:}16{.}934 \dashrightarrow 00{:}39{:}19{.}764$  in one of these genes and these

NOTE Confidence: 0.807376979090909

 $00:39:19.764 \rightarrow 00:39:22.590$  individuals have present this syndrome

NOTE Confidence: 0.807376979090909

 $00:39:22.590 \rightarrow 00:39:25.635$  presents as penetrance about 70 to 80%,

NOTE Confidence: 0.807376979090909

 $00{:}39{:}25.640 \dashrightarrow 00{:}39{:}26.756$  which means that.

NOTE Confidence: 0.807376979090909

 $00{:}39{:}26.756 \dashrightarrow 00{:}39{:}29.989$  That in in 70 to 80% of the cases

NOTE Confidence: 0.807376979090909

 $00{:}39{:}29{.}989 \dashrightarrow 00{:}39{:}31{.}654$  individuals that carry a mutation,

NOTE Confidence: 0.807376979090909

00:39:31.660 - 00:39:32.900 they end up developing

 $00:39:32.900 \rightarrow 00:39:34.450$  cancer and when they develop,

NOTE Confidence: 0.807376979090909

 $00{:}39{:}34{.}450 \dashrightarrow 00{:}39{:}36{.}050$  cancer is usually associated

NOTE Confidence: 0.807376979090909

 $00:39:36.050 \longrightarrow 00:39:38.450$  with an early age of onset.

NOTE Confidence: 0.807376979090909

00:39:38.450 --> 00:39:39.376 So clinically,

NOTE Confidence: 0.807376979090909

 $00{:}39{:}39{.}376 \dashrightarrow 00{:}39{:}41.691$  Lynch syndrome patients present with

NOTE Confidence: 0.807376979090909

 $00{:}39{:}41.691 \dashrightarrow 00{:}39{:}44.336$  fewer polyps than other colorectal

NOTE Confidence: 0.807376979090909

00:39:44.336 --> 00:39:46.109 cancer inherited syndromes,

NOTE Confidence: 0.807376979090909

 $00{:}39{:}46{.}110 \dashrightarrow 00{:}39{:}47{.}700$  and the tumors localized in

NOTE Confidence: 0.807376979090909

 $00:39:47.700 \longrightarrow 00:39:49.810$  the right side of the column.

NOTE Confidence: 0.807376979090909

 $00:39:49.810 \longrightarrow 00:39:51.030$  And this lynch patients.

NOTE Confidence: 0.807376979090909

 $00:39:51.030 \longrightarrow 00:39:52.860$  They have a high risk of

NOTE Confidence: 0.807376979090909

 $00:39:52.925 \rightarrow 00:39:54.668$  developing multiple cancers.

NOTE Confidence: 0.807376979090909

00:39:54.670 --> 00:39:55.972 Colorectal cancers are

NOTE Confidence: 0.807376979090909

 $00:39:55.972 \longrightarrow 00:39:57.708$  diagnosis or over time.

NOTE Confidence: 0.807376979090909

 $00{:}39{:}57{.}710 \dashrightarrow 00{:}39{:}59{.}594$  And another clinical feature

NOTE Confidence: 0.807376979090909

 $00:39:59.594 \rightarrow 00:40:01.949$  that it's important to remember.

- NOTE Confidence: 0.807376979090909
- 00:40:01.950 --> 00:40:02.372 Sorry,
- NOTE Confidence: 0.807376979090909
- $00{:}40{:}02{.}372 \dashrightarrow 00{:}40{:}04{.}482$  remember from these patients is
- NOTE Confidence: 0.807376979090909
- $00:40:04.482 \longrightarrow 00:40:07.119$  that the Lynch syndrome is actually
- NOTE Confidence: 0.807376979090909
- 00:40:07.119 --> 00:40:09.309 a multi cancer syndrome affecting
- NOTE Confidence: 0.807376979090909
- $00{:}40{:}09{.}310 \dashrightarrow 00{:}40{:}10{.}948$  different organs and here you can
- NOTE Confidence: 0.807376979090909
- $00:40:10.948 \longrightarrow 00:40:12.924$  see the list and it's significantly
- NOTE Confidence: 0.807376979090909
- $00:40:12.924 \longrightarrow 00:40:14.974$  important to remember that because
- NOTE Confidence: 0.807376979090909
- $00:40:14.974 \rightarrow 00:40:16.961$  actually female lynch patients they
- NOTE Confidence: 0.807376979090909
- $00:40:16.961 \rightarrow 00:40:19.390$  developed for example like in the material,
- NOTE Confidence: 0.807376979090909
- $00:40:19.390 \longrightarrow 00:40:21.045$  they have a higher incidence
- NOTE Confidence: 0.807376979090909
- 00:40:21.045 00:40:22.369 of developing endometrial than
- NOTE Confidence: 0.807376979090909
- $00{:}40{:}22{.}369 \dashrightarrow 00{:}40{:}23{.}080$  colorectal cancer.
- NOTE Confidence: 0.77898428696
- 00:40:25.090 --> 00:40:27.178 So because I explained you that
- NOTE Confidence: 0.77898428696
- $00{:}40{:}27.178 \dashrightarrow 00{:}40{:}29.449$  Link syndrome is the most common
- NOTE Confidence: 0.77898428696
- 00:40:29.449 --> 00:40:31.459 cancer syndrome and because of
- NOTE Confidence: 0.77898428696

 $00:40:31.459 \longrightarrow 00:40:33.621$  all this clinical features that

NOTE Confidence: 0.77898428696

 $00:40:33.621 \longrightarrow 00:40:35.365$  these patients have nowadays,

NOTE Confidence: 0.77898428696

 $00:40:35.365 \longrightarrow 00:40:37.855$  all in the midfield and Jay

NOTE Confidence: 0.77898428696

 $00:40:37.855 \rightarrow 00:40:40.439$  cancers are are supposed to be

NOTE Confidence: 0.77898428696

 $00{:}40{:}40{.}439 \dashrightarrow 00{:}40{:}42{.}947$  tested for the for Lynn syndrome.

NOTE Confidence: 0.77898428696

 $00{:}40{:}42.950 \dashrightarrow 00{:}40{:}46.333$  So how this works is all these cancers.

NOTE Confidence: 0.77898428696

00:40:46.333 --> 00:40:48.638 They are tested with immunohistochemistry

NOTE Confidence: 0.77898428696

 $00:40:48.638 \rightarrow 00:40:51.629$  for the expression of the four main

NOTE Confidence: 0.77898428696

 $00{:}40{:}51.629 \dashrightarrow 00{:}40{:}54.067$  proteins of the mismatch repair if.

NOTE Confidence: 0.77898428696

 $00{:}40{:}54.067 \dashrightarrow 00{:}40{:}56.689$  Because of the expression in MSH

NOTE Confidence: 0.77898428696

00:40:56.689 --> 00:40:59.581 2 MSH 6 or PS2 is identified,

NOTE Confidence: 0.77898428696

 $00{:}40{:}59{.}581 \dashrightarrow 00{:}41{:}02{.}143$  then the patient should be referred

NOTE Confidence: 0.77898428696

 $00{:}41{:}02{.}143 \dashrightarrow 00{:}41{:}04{.}974$  to cancer genetics for testing and

NOTE Confidence: 0.77898428696

 $00:41:04.974 \longrightarrow 00:41:06.798$  contrary if the loss of emulate

NOTE Confidence: 0.77898428696

 $00{:}41{:}06.798 \dashrightarrow 00{:}41{:}08.716$  one or PMS or the conduction

NOTE Confidence: 0.77898428696

 $00:41:08.716 \longrightarrow 00:41:10.893$  of emulate one and PMS two is

- NOTE Confidence: 0.77898428696
- $00:41:10.962 \rightarrow 00:41:13.278$  identified by immunohistochemistry,
- NOTE Confidence: 0.77898428696
- $00{:}41{:}13.280 \dashrightarrow 00{:}41{:}15.400$  then there is the one.
- NOTE Confidence: 0.77898428696
- 00:41:15.400 00:41:17.120 Methylation should be tested and
- NOTE Confidence: 0.77898428696
- $00:41:17.120 \longrightarrow 00:41:19.239$  if there is no methylation then
- NOTE Confidence: 0.77898428696
- $00{:}41{:}19{.}239 \dashrightarrow 00{:}41{:}20{.}929$  the patient should be referred
- NOTE Confidence: 0.77898428696
- $00:41:20.929 \longrightarrow 00:41:22.912$  to cancer genetics and in any
- NOTE Confidence: 0.77898428696
- $00:41:22.912 \longrightarrow 00:41:24.616$  way if anyone in the identifies.
- NOTE Confidence: 0.77898428696
- $00:41:24.620 \longrightarrow 00:41:28.046$  MSI case, but there was no.
- NOTE Confidence: 0.77898428696
- 00:41:28.050 --> 00:41:29.958 I'm even Histochemistry tested,
- NOTE Confidence: 0.77898428696
- $00{:}41{:}29{.}958 \dashrightarrow 00{:}41{:}33{.}470$  but the physicians have a clinical concern.
- NOTE Confidence: 0.77898428696
- $00:41:33.470 \longrightarrow 00:41:35.195$  Then these patients should be
- NOTE Confidence: 0.77898428696
- $00:41:35.195 \longrightarrow 00:41:36.575$  preferred to cancer genetics.
- NOTE Confidence: 0.682636668333333
- $00{:}41{:}38{.}730 \dashrightarrow 00{:}41{:}41{.}054$  So in general, in the cancer genetics
- NOTE Confidence: 0.682636668333333
- 00:41:41.054 --> 00:41:42.850 clinic was we've been facing,
- NOTE Confidence: 0.682636668333333
- $00:41:42.850 \longrightarrow 00:41:46.066$  is that about 50% of the suspected link
- NOTE Confidence: 0.682636668333333

 $00:41:46.066 \rightarrow 00:41:48.210$  syndrome patients that are referred.

NOTE Confidence: 0.682636668333333

 $00{:}41{:}48{.}210 \dashrightarrow 00{:}41{:}51{.}633$  They actually test negative for Jim for

NOTE Confidence: 0.682636668333333

00:41:51.633 --> 00:41:53.943 having germline mutations in the genes. NOTE Confidence: 0.682636668333333

00:41:53.943 --> 00:41:56.447 And this case is where name as Lynch

NOTE Confidence: 0.682636668333333

00:41:56.447 --> 00:41:58.752 like syndrome because they are similar

NOTE Confidence: 0.682636668333333

 $00:41:58.752 \rightarrow 00:42:01.590$  to lynch like but there's no mutations.

NOTE Confidence: 0.682636668333333

 $00{:}42{:}01{.}590 \dashrightarrow 00{:}42{:}04{.}229$  So as as a definition these lines

NOTE Confidence: 0.682636668333333

 $00:42:04.229 \rightarrow 00:42:06.050$  like syndrome patient patients,

NOTE Confidence: 0.682636668333333

 $00:42:06.050 \rightarrow 00:42:08.606$  they develop tumors at the MSI.

NOTE Confidence: 0.682636668333333

 $00:42:08.610 \rightarrow 00:42:10.647$  They don't have resolution of image one.

NOTE Confidence: 0.682636668333333

 $00:42:10.650 \longrightarrow 00:42:12.870$  They don't have the hotspot be

NOTE Confidence: 0.682636668333333

 $00{:}42{:}12{.}870 \dashrightarrow 00{:}42{:}14{.}863$ 600 imitations and they don't

NOTE Confidence: 0.682636668333333

 $00{:}42{:}14.863 \dashrightarrow 00{:}42{:}17.088$  have a germline mutations either.

NOTE Confidence: 0.682636668333333

 $00:42:17.090 \rightarrow 00:42:20.346$  So what are these things like cases they

NOTE Confidence: 0.682636668333333

 $00:42:20.346 \rightarrow 00:42:23.010$  actually could be Lynch syndrome cases,

NOTE Confidence: 0.682636668333333

 $00:42:23.010 \longrightarrow 00:42:25.050$  but that due to difficulty on
- NOTE Confidence: 0.682636668333333
- $00:42:25.050 \rightarrow 00:42:26.882$  identifying mutations or because they
- NOTE Confidence: 0.682636668333333
- $00{:}42{:}26.882 \dashrightarrow 00{:}42{:}28.546$  have like encrypting mitigations.
- NOTE Confidence: 0.682636668333333
- $00{:}42{:}28.550 \dashrightarrow 00{:}42{:}30.468$  Maybe we have not been able to
- NOTE Confidence: 0.682636668333333
- $00:42:30.468 \longrightarrow 00:42:31.290$  then defy them,
- NOTE Confidence: 0.682636668333333
- $00:42:31.290 \longrightarrow 00:42:33.900$  or they could actually be heritary
- NOTE Confidence: 0.682636668333333
- $00{:}42{:}33{.}900 \dashrightarrow 00{:}42{:}36{.}790$  cases that they might be due to general
- NOTE Confidence: 0.682636668333333
- $00:42:36.790 \rightarrow 00:42:38.740$  mutations in other genes and that.
- NOTE Confidence: 0.682636668333333
- $00{:}42{:}38.740 \dashrightarrow 00{:}42{:}43.556$  They end up developing MSI as a driver
- NOTE Confidence: 0.682636668333333
- 00:42:43.556 --> 00:42:48.738 effect, not as a cancer driver effect,
- NOTE Confidence: 0.682636668333333
- 00:42:48.740 --> 00:42:51.090 sorry.
- NOTE Confidence: 0.682636668333333
- $00:42:51.090 \rightarrow 00:42:53.800$  Sorry that they developed because
- NOTE Confidence: 0.682636668333333
- $00:42:53.800 \longrightarrow 00:42:56.510$  other germline mutations but they
- NOTE Confidence: 0.682636668333333
- $00{:}42{:}56{.}595 \dashrightarrow 00{:}42{:}59{.}535$  actually the MSI was an effect of
- NOTE Confidence: 0.682636668333333
- $00:42:59.535 \rightarrow 00:43:02.310$  the development of cancer but they
- NOTE Confidence: 0.682636668333333
- $00:43:02.310 \longrightarrow 00:43:04.685$  could just be sporadic cancers.
- NOTE Confidence: 0.682636668333333

 $00:43:04.690 \rightarrow 00:43:07.930$  So to address these challenges,

NOTE Confidence: 0.682636668333333

 $00:43:07.930 \longrightarrow 00:43:10.888$  we have developed 2 main projects,

NOTE Confidence: 0.682636668333333

 $00:43:10.890 \longrightarrow 00:43:12.882$  one and the general level and

NOTE Confidence: 0.682636668333333

 $00:43:12.882 \longrightarrow 00:43:15.320$  another one at the semantic level.

NOTE Confidence: 0.682636668333333

 $00{:}43{:}15{.}320 \dashrightarrow 00{:}43{:}17{.}413$  The general level with our aim was

NOTE Confidence: 0.682636668333333

 $00{:}43{:}17{.}413 \dashrightarrow 00{:}43{:}19{.}200$  to identify the current deficient

NOTE Confidence: 0.682636668333333

 $00{:}43{:}19{.}200 \dashrightarrow 00{:}43{:}21{.}678$  DNA repair genes and the cellular

NOTE Confidence: 0.682636668333333

 $00:43:21.678 \rightarrow 00:43:23.716$  consequences that contribute to the

NOTE Confidence: 0.682636668333333

 $00:43:23.716 \longrightarrow 00:43:25.631$  development of colorectal cancer in

NOTE Confidence: 0.682636668333333

 $00:43:25.631 \rightarrow 00:43:28.860$  lines like patients and at the somatic level,

NOTE Confidence: 0.682636668333333

 $00:43:28.860 \rightarrow 00:43:31.356$  we aim to define molecular factors

NOTE Confidence: 0.682636668333333

 $00:43:31.356 \rightarrow 00:43:34.050$  in the three types of mismatch.

NOTE Confidence: 0.682636668333333

 $00:43:34.050 \rightarrow 00:43:36.402$  Deficient tumors the lynch like

NOTE Confidence: 0.682636668333333

 $00:43:36.402 \rightarrow 00:43:39.321$  and the viral methylated ones which will

NOTE Confidence: 0.682636668333333

 $00:43:39.321 \longrightarrow 00:43:41.456$  contribute to diagnosis and treatment.

NOTE Confidence: 0.523577779909091

 $00{:}43{:}43{.}550 \dashrightarrow 00{:}43{:}46{.}646$  So so our collaborations with the

- NOTE Confidence: 0.523577779909091
- $00{:}43{:}46.646 \dashrightarrow 00{:}43{:}49.610$  correct with the current concerns,
- NOTE Confidence: 0.523577779909091
- $00:43:49.610 \longrightarrow 00:43:52.298$  we were able to describe the patients have
- NOTE Confidence: 0.523577779909091
- $00:43:52.298 \rightarrow 00:43:55.314$  a higher frequency of family history of
- NOTE Confidence: 0.523577779909091
- $00:43:55.314 \rightarrow 00:43:57.589$  colorectal cancer than sporadic cases,
- NOTE Confidence: 0.523577779909091
- $00:43:57.590 \rightarrow 00:44:00.894$  and you can see here how the standardized
- NOTE Confidence: 0.523577779909091
- $00{:}44{:}00{.}894 \dashrightarrow 00{:}44{:}03{.}930$  incidence ratio was 2.2 for the links in
- NOTE Confidence: 0.523577779909091
- 00:44:03.930 --> 00:44:07.664 comparison to 0.48 for sporadic individuals,
- NOTE Confidence: 0.523577779909091
- $00{:}44{:}07.664 \dashrightarrow 00{:}44{:}11.072$  and and these incidents
- NOTE Confidence: 0.523577779909091
- $00:44:11.072 \longrightarrow 00:44:12.840$  of family history was.
- NOTE Confidence: 0.523577779909091
- $00:44:12.840 \longrightarrow 00:44:14.308$  Actually lower than lead,
- NOTE Confidence: 0.523577779909091
- $00:44:14.308 \longrightarrow 00:44:16.143$  so this kind of foods.
- NOTE Confidence: 0.523577779909091
- $00:44:16.150 \longrightarrow 00:44:19.080$  The Linge like phenotype and
- NOTE Confidence: 0.523577779909091
- $00:44:19.080 \longrightarrow 00:44:20.838$  in between between.
- NOTE Confidence: 0.523577779909091
- $00{:}44{:}20{.}840 \dashrightarrow 00{:}44{:}22{.}622$  Lynch and Sprite.
- NOTE Confidence: 0.523577779909091
- $00{:}44{:}22.622 \dashrightarrow 00{:}44{:}27.216$  We're also able to to show that the
- NOTE Confidence: 0.523577779909091

00:44:27.216 --> 00:44:30.704 average age of diagnosis for Lynch like is

NOTE Confidence: 0.523577779909091

00:44:30.704 --> 00:44:33.250 significantly younger than sporadic cases.

NOTE Confidence: 0.523577779909091

 $00{:}44{:}33{.}250 \dashrightarrow 00{:}44{:}35{.}746$  So these two features are suggest

NOTE Confidence: 0.523577779909091

 $00:44:35.746 \rightarrow 00:44:37.889$  that a potential unidentified genetic

NOTE Confidence: 0.523577779909091

 $00:44:37.889 \rightarrow 00:44:40.773$  predisposition induced in this in a group,

NOTE Confidence: 0.523577779909091

 $00:44:40.780 \longrightarrow 00:44:43.828$  at least in Group of Lynch

NOTE Confidence: 0.523577779909091

 $00:44:43.828 \longrightarrow 00:44:45.352$  like syndrome patients.

NOTE Confidence: 0.523577779909091

 $00:44:45.360 \longrightarrow 00:44:46.504$  So to address this,

NOTE Confidence: 0.523577779909091

 $00:44:46.504 \rightarrow 00:44:48.939$  and because we believe that that is the case,

NOTE Confidence: 0.523577779909091

 $00:44:48.940 \longrightarrow 00:44:54.886$  we develop a a study including 654

NOTE Confidence: 0.523577779909091

 $00{:}44{:}54{.}886 \dashrightarrow 00{:}44{:}57{.}516$  individuals from our Chicago Colorectal

NOTE Confidence: 0.523577779909091

00:44:57.516 --> 00:44:59.620 Cancer Center consortium cohort,

NOTE Confidence: 0.523577779909091

 $00{:}44{:}59{.}620 \dashrightarrow 00{:}45{:}02{.}698$  and we performed that link screening

NOTE Confidence: 0.523577779909091

 $00{:}45{:}02.700 \dashrightarrow 00{:}45{:}05.680$  testing that I mentioned before

NOTE Confidence: 0.523577779909091

 $00:45:05.680 \longrightarrow 00:45:08.620$  we identified 23 suspected links.

NOTE Confidence: 0.523577779909091

00:45:08.620 --> 00:45:09.730 Lynn syndrome.

 $00{:}45{:}11.770 \dashrightarrow 00{:}45{:}15.567$  So from those we were able to have

NOTE Confidence: 0.865651094285714

 $00{:}45{:}15{.}567 \dashrightarrow 00{:}45{:}17{.}926$  germline DNA from 15 of them and

NOTE Confidence: 0.865651094285714

 $00:45:17.926 \rightarrow 00:45:20.194$  we perform XM sequencing and we

NOTE Confidence: 0.865651094285714

 $00{:}45{:}20.194 \dashrightarrow 00{:}45{:}22.468$  identified that four of them were

NOTE Confidence: 0.865651094285714

 $00:45:22.548 \rightarrow 00:45:25.164$  actually engaged and eleven were links

NOTE Confidence: 0.865651094285714

 $00{:}45{:}25{.}164 \dashrightarrow 00{:}45{:}27{.}912$  like were classified as Lynch like

NOTE Confidence: 0.865651094285714

 $00{:}45{:}27{.}912 \dashrightarrow 00{:}45{:}30{.}417$  because we didn't find limitations.

NOTE Confidence: 0.865651094285714

 $00:45:30.420 \longrightarrow 00:45:33.156$  So then we take it one step further

NOTE Confidence: 0.865651094285714

 $00{:}45{:}33{.}156 \dashrightarrow 00{:}45{:}36{.}212$  and we wanted to identify if if

NOTE Confidence: 0.865651094285714

00:45:36.212 --> 00:45:38.730 any of these links, like patients,

NOTE Confidence: 0.865651094285714

 $00:45:38.730 \longrightarrow 00:45:41.775$  had mutations in other DNA repair genes.

NOTE Confidence: 0.865651094285714

 $00{:}45{:}41.780 \dashrightarrow 00{:}45{:}45.630$  So we analyze 162 DNA repair genes and

NOTE Confidence: 0.865651094285714

 $00{:}45{:}45{.}630 \dashrightarrow 00{:}45{:}48{.}668$  we were able to see that this links,

NOTE Confidence: 0.865651094285714

 $00{:}45{:}48.668 \dashrightarrow 00{:}45{:}49.620$  like patients.

NOTE Confidence: 0.865651094285714

 $00{:}45{:}49{.}620 \dashrightarrow 00{:}45{:}51{.}996$  They had the higher mutational burden

 $00:45:52.000 \rightarrow 00:45:54.576$  and comparison to lynch to the TCG,

NOTE Confidence: 0.865651094285714

00:45:54.580 --> 00:45:56.868 a colorectal cancer cohort,

NOTE Confidence: 0.865651094285714

 $00{:}45{:}56{.}868 \dashrightarrow 00{:}45{:}59{.}728$  and to control without cancer.

NOTE Confidence: 0.865651094285714

 $00:45:59.730 \longrightarrow 00:46:00.514$  So specifically,

NOTE Confidence: 0.865651094285714

 $00:46:00.514 \rightarrow 00:46:03.258$  we identified four loss of function variants,

NOTE Confidence: 0.865651094285714

 $00:46:03.260 \rightarrow 00:46:06.004$  one in body, one one in Werner,

NOTE Confidence: 0.865651094285714

 $00:46:06.010 \longrightarrow 00:46:10.717$  one in MCPH one and one in Rev 3.

NOTE Confidence: 0.865651094285714

 $00:46:10.720 \longrightarrow 00:46:12.754$  So then after this first study

NOTE Confidence: 0.865651094285714

 $00:46:12.754 \longrightarrow 00:46:14.507$  that we identified that links

NOTE Confidence: 0.865651094285714

 $00{:}46{:}14.507 \dashrightarrow 00{:}46{:}16.499$  like were in bridge with mutations

NOTE Confidence: 0.865651094285714

 $00:46:16.499 \longrightarrow 00:46:18.320$  in the inner river jeans,

NOTE Confidence: 0.865651094285714

 $00{:}46{:}18.320 \dashrightarrow 00{:}46{:}20.756$  we include decided to include two

NOTE Confidence: 0.865651094285714

00:46:20.756 --> 00:46:22.820 different independent series of lines,

NOTE Confidence: 0.865651094285714

00:46:22.820 --> 00:46:25.448 like patients to try to identify

NOTE Confidence: 0.865651094285714

 $00:46:25.448 \rightarrow 00:46:28.243$  genes that maybe would be recurrently

NOTE Confidence: 0.865651094285714

 $00:46:28.243 \rightarrow 00:46:30.787$  mutated in this in this phenotype.

 $00:46:30.787 \longrightarrow 00:46:33.904$  So when we did that in the first

NOTE Confidence: 0.865651094285714

 $00:46:33.904 \longrightarrow 00:46:36.487$  series with unified 6 genes that

NOTE Confidence: 0.865651094285714

 $00:46:36.487 \longrightarrow 00:46:38.449$  were mutated and had lots of

NOTE Confidence: 0.865651094285714

 $00:46:38.449 \rightarrow 00:46:40.330$  function variants and interestingly.

NOTE Confidence: 0.865651094285714

 $00{:}46{:}40{.}330 \dashrightarrow 00{:}46{:}42{.}988$  We found the same splicing variant

NOTE Confidence: 0.865651094285714

 $00:46:42.988 \longrightarrow 00:46:45.458$  in two different patients in the

NOTE Confidence: 0.865651094285714

 $00:46:45.458 \longrightarrow 00:46:47.665$  regular 5 gene and we actually

NOTE Confidence: 0.865651094285714

 $00{:}46{:}47.665 \dashrightarrow 00{:}46{:}50.215$  perform a kinship analysis to show

NOTE Confidence: 0.865651094285714

 $00{:}46{:}50{.}215 \dashrightarrow 00{:}46{:}53{.}406$  that and to prove that these two

NOTE Confidence: 0.865651094285714

 $00:46:53.406 \rightarrow 00:46:55.198$  patients were not genetically.

NOTE Confidence: 0.865651094285714

 $00:46:55.200 \rightarrow 00:46:56.860$  And they were not genetically.

NOTE Confidence: 0.651248294

 $00{:}47{:}02{.}480 \dashrightarrow 00{:}47{:}04{.}520$  There were no this related.

NOTE Confidence: 0.651248294

 $00:47:04.520 \rightarrow 00:47:06.640$  Sorry, because these patients were

NOTE Confidence: 0.651248294

 $00{:}47{:}06.640 \dashrightarrow 00{:}47{:}09.774$  both coming from from Spain and we just

NOTE Confidence: 0.651248294

 $00{:}47{:}09{.}774 \dashrightarrow 00{:}47{:}12{.}254$  wanted to make sure that there was no

 $00:47:12.254 \rightarrow 00:47:15.976$  any family relation that we don't know.

NOTE Confidence: 0.651248294

 $00{:}47{:}15{.}980 \dashrightarrow 00{:}47{:}18{.}059$  And then when we developed the analysis

NOTE Confidence: 0.651248294

 $00:47:18.059 \longrightarrow 00:47:20.099$  of the other series of patients,

NOTE Confidence: 0.651248294

 $00:47:20.100 \longrightarrow 00:47:22.945$  we again identified another loss

NOTE Confidence: 0.651248294

 $00:47:22.945 \longrightarrow 00:47:26.070$  of function variant in regular 5.

NOTE Confidence: 0.651248294

 $00{:}47{:}26.070 \dashrightarrow 00{:}47{:}28.303$  So with that, if you've been able NOTE Confidence: 0.651248294

 $00:47:28.303 \longrightarrow 00:47:31.138$  to follow my my talk and the the

NOTE Confidence: 0.651248294

 $00{:}47{:}31{.}138 \dashrightarrow 00{:}47{:}32{.}582$  the notification of mutations

NOTE Confidence: 0.651248294

 $00{:}47{:}32{.}582 \dashrightarrow 00{:}47{:}34{.}470$  in our original serious,

NOTE Confidence: 0.651248294

 $00:47:34.470 \longrightarrow 00:47:37.155$  we have identified 4 different

NOTE Confidence: 0.651248294

 $00{:}47{:}37{.}155 \dashrightarrow 00{:}47{:}40{.}442$  mutations in genes that belong to

NOTE Confidence: 0.651248294

00:47:40.442 --> 00:47:43.007 the Dracula DNA helicase family.

NOTE Confidence: 0.651248294

 $00{:}47{:}43.010 \dashrightarrow 00{:}47{:}46.645$  So here you can see the five the

NOTE Confidence: 0.651248294

 $00:47:46.645 \longrightarrow 00:47:49.135$  five proteins that are in this

NOTE Confidence: 0.651248294

00:47:49.135 --> 00:47:51.243 family regular one bloom Werner

NOTE Confidence: 0.651248294

 $00:47:51.243 \rightarrow 00:47:53.980$  regular four and regular 5 and all

- NOTE Confidence: 0.651248294
- $00:47:53.980 \longrightarrow 00:47:56.790$  of them share the same helicase.
- NOTE Confidence: 0.651248294
- 00:47:56.790 --> 00:47:57.800 I mean.
- NOTE Confidence: 0.651248294
- $00:47:57.800 \longrightarrow 00:47:59.295$  So these are the individuals
- NOTE Confidence: 0.651248294
- $00{:}47{:}59{.}295 \dashrightarrow 00{:}48{:}01{.}200$  that we have identified the two
- NOTE Confidence: 0.651248294
- $00:48:01.200 \rightarrow 00:48:02.940$  individuals with the same splicing,
- NOTE Confidence: 0.651248294
- $00{:}48{:}02{.}940 \dashrightarrow 00{:}48{:}04{.}875$  one with the insertion and
- NOTE Confidence: 0.651248294
- $00:48:04.875 \longrightarrow 00:48:06.423$  from the original cohort.
- NOTE Confidence: 0.651248294
- $00{:}48{:}06{.}430 \dashrightarrow 00{:}48{:}08{.}970$  We also identified this individual
- NOTE Confidence: 0.651248294
- $00{:}48{:}08{.}970 \dashrightarrow 00{:}48{:}10{.}494$  with a mutation.
- NOTE Confidence: 0.651248294
- $00{:}48{:}10.500 \dashrightarrow 00{:}48{:}13.230$  So after that we were interested in
- NOTE Confidence: 0.651248294
- 00:48:13.230 --> 00:48:15.600 knowing if maybe the mutations in
- NOTE Confidence: 0.651248294
- $00{:}48{:}15{.}600 \dashrightarrow 00{:}48{:}18{.}600$  this in this family of genes were also
- NOTE Confidence: 0.651248294
- $00:48:18.600 \longrightarrow 00:48:21.280$  recurring in other cancer friendships.
- NOTE Confidence: 0.651248294
- $00:48:21.280 \longrightarrow 00:48:22.788$  So to do that?
- NOTE Confidence: 0.651248294
- $00{:}48{:}22.788 \dashrightarrow 00{:}48{:}24.673$  First took individuals that were
- NOTE Confidence: 0.651248294

 $00{:}48{:}24.673 \dashrightarrow 00{:}48{:}26.769$  referred to the Smilo Cancer

NOTE Confidence: 0.651248294

 $00{:}48{:}26.769 \dashrightarrow 00{:}48{:}28.413$  Genetics and Prevention program

NOTE Confidence: 0.651248294

 $00:48:28.413 \longrightarrow 00:48:30.589$  that when they were referred,

NOTE Confidence: 0.651248294

 $00:48:30.590 \longrightarrow 00:48:32.450$  they and they were tested

NOTE Confidence: 0.651248294

 $00{:}48{:}32{.}450 \dashrightarrow 00{:}48{:}34{.}310$  and we in the clinic.

NOTE Confidence: 0.651248294

00:48:34.310 --> 00:48:35.780 They didn't find any mutations,

NOTE Confidence: 0.651248294

00:48:35.780 --> 00:48:39.446 say many known cancer predisposition genes.

NOTE Confidence: 0.651248294

 $00:48:39.450 \longrightarrow 00:48:43.018$  So we perform XM sequencing in 156

NOTE Confidence: 0.651248294

00:48:43.018 --> 00:48:46.184 breast cancer patients in 75 individuals

NOTE Confidence: 0.651248294

 $00{:}48{:}46{.}184 \dashrightarrow 00{:}48{:}49{.}346$  that had different types of tumors

NOTE Confidence: 0.651248294

 $00{:}48{:}49{.}346 \dashrightarrow 00{:}48{:}52{.}342$  that were not breast breast tumors.

NOTE Confidence: 0.651248294

 $00:48:52.342 \longrightarrow 00:48:53.770$  We'll sync clouded,

NOTE Confidence: 0.651248294

 $00{:}48{:}53.770 \dashrightarrow 00{:}48{:}55.015$  MSH and PC.

NOTE Confidence: 0.651248294

 $00{:}48{:}55.015 \dashrightarrow 00{:}48{:}58.873$  These are very rare type of familial

NOTE Confidence: 0.651248294

 $00{:}48{:}58.873 \dashrightarrow 00{:}49{:}02.172$  colorectal cancer that affects individuals

NOTE Confidence: 0.651248294

 $00:49:02.172 \longrightarrow 00:49:04.032$  in different generations and that

- NOTE Confidence: 0.651248294
- $00:49:04.032 \rightarrow 00:49:06.339$  they develop cancer at the young age.
- NOTE Confidence: 0.651248294
- $00{:}49{:}06{.}340 \dashrightarrow 00{:}49{:}09{.}658$  But these individuals don't have MSI RMS.
- NOTE Confidence: 0.651248294
- 00:49:09.660 --> 00:49:10.536 And lastly,
- NOTE Confidence: 0.651248294
- $00:49:10.536 \rightarrow 00:49:14.040$  we also identify mutations in the DC G.
- NOTE Confidence: 0.651248294
- $00:49:14.040 \longrightarrow 00:49:15.930$  So with this analysis we were
- NOTE Confidence: 0.651248294
- $00:49:15.930 \longrightarrow 00:49:17.880$  able to see that actually,
- NOTE Confidence: 0.651248294
- $00:49:17.880 \rightarrow 00:49:20.456$  like the higher a little frequency variants
- NOTE Confidence: 0.651248294
- 00:49:20.456 --> 00:49:23.110 in DNA repair genes that are not the.
- NOTE Confidence: 0.651248294
- $00{:}49{:}23.110 \dashrightarrow 00{:}49{:}26.225$  Compare and then they are not know
- NOTE Confidence: 0.651248294
- 00:49:26.225 --> 00:49:28.286 well established cancer predisposing
- NOTE Confidence: 0.651248294
- $00:49:28.286 \longrightarrow 00:49:31.784$  genes and we all the identified
- NOTE Confidence: 0.651248294
- $00{:}49{:}31.784 \dashrightarrow 00{:}49{:}35.067$  mutations in the REQ DNA helicases
- NOTE Confidence: 0.651248294
- $00:49:35.067 \longrightarrow 00:49:37.597$  in the lynch like phenotype.
- NOTE Confidence: 0.651248294
- $00{:}49{:}37{.}600 \dashrightarrow 00{:}49{:}41{.}580$  So then we went back to the
- NOTE Confidence: 0.651248294
- $00:49:41.580 \longrightarrow 00:49:44.379$  families that we were able to.
- NOTE Confidence: 0.651248294

 $00:49:44.380 \longrightarrow 00:49:46.588$  Contact again to in the defy

NOTE Confidence: 0.651248294

 $00{:}49{:}46.588 \dashrightarrow 00{:}49{:}48.650$  if the mutations were shared.

NOTE Confidence: 0.651248294

 $00{:}49{:}48.650 \dashrightarrow 00{:}49{:}50.375$  If these mutations with shared

NOTE Confidence: 0.651248294

 $00:49:50.375 \rightarrow 00:49:51.755$  with other family members,

NOTE Confidence: 0.651248294

 $00{:}49{:}51{.}760 \dashrightarrow 00{:}49{:}53{.}928$  so here these are the three families that

NOTE Confidence: 0.651248294

 $00:49:53.928 \rightarrow 00:49:56.167$  will have with mutations in the right QL.

NOTE Confidence: 0.651248294

00:49:56.170 --> 00:49:59.058 So family A&B are the the ones that

NOTE Confidence: 0.651248294

 $00:49:59.058 \rightarrow 00:50:00.858$  share the same splicing variant,

NOTE Confidence: 0.651248294

 $00{:}50{:}00{.}858 \dashrightarrow 00{:}50{:}03{.}196$  so here this is the program that

NOTE Confidence: 0.651248294

 $00:50:03.196 \longrightarrow 00:50:05.121$  developed for family aid that

NOTE Confidence: 0.651248294

 $00:50:05.121 \dashrightarrow 00:50:06.267$  developed colorectal cancer.

NOTE Confidence: 0.651248294

 $00{:}50{:}06{.}270 \dashrightarrow 00{:}50{:}06{.}928$  At 63.

NOTE Confidence: 0.651248294

 $00{:}50{:}06{.}928 \dashrightarrow 00{:}50{:}08{.}902$  We were also able to sequence

NOTE Confidence: 0.651248294

 $00:50:08.902 \longrightarrow 00:50:11.215$  the tumor of this individual and

NOTE Confidence: 0.651248294

 $00{:}50{:}11.215 \dashrightarrow 00{:}50{:}13.579$  we also found a missense variant

NOTE Confidence: 0.651248294

 $00:50:13.653 \rightarrow 00:50:15.655$  in the in the tumor of this.

- NOTE Confidence: 0.651248294
- $00:50:15.660 \longrightarrow 00:50:16.809$  Of this patient,
- NOTE Confidence: 0.651248294
- $00{:}50{:}16.809 \dashrightarrow 00{:}50{:}19.490$  and then the brother of this program
- NOTE Confidence: 0.651248294
- $00{:}50{:}19{.}569 \dashrightarrow 00{:}50{:}22{.}001$  had a small bowel cancer and he was
- NOTE Confidence: 0.651248294
- $00:50:22.001 \rightarrow 00:50:24.418$  also a carrier of the mutation.
- NOTE Confidence: 0.651248294
- $00:50:24.420 \longrightarrow 00:50:25.636$  The family we we.
- NOTE Confidence: 0.651248294
- $00:50:25.636 \longrightarrow 00:50:27.460$  This was the program that they
- NOTE Confidence: 0.651248294
- $00:50:27.530 \longrightarrow 00:50:29.180$  are of collector cancer at
- NOTE Confidence: 0.815990964416667
- 00:50:29.180 --> 00:50:31.755 64 very strong family history
- NOTE Confidence: 0.815990964416667
- $00{:}50{:}31.755 \dashrightarrow 00{:}50{:}35.319$  and then we tested the two sons.
- NOTE Confidence: 0.815990964416667
- $00:50:35.320 \longrightarrow 00:50:37.259$  That one was a carrier and the
- NOTE Confidence: 0.815990964416667
- $00:50:37.259 \rightarrow 00:50:39.696$  other one was not a carrier and the
- NOTE Confidence: 0.815990964416667
- $00:50:39.696 \rightarrow 00:50:41.560$  rate of diagnosis was under 40s.
- NOTE Confidence: 0.815990964416667
- $00{:}50{:}41{.}560 \dashrightarrow 00{:}50{:}44{.}176$  And lastly this last one we.
- NOTE Confidence: 0.815990964416667
- $00{:}50{:}44.180 \dashrightarrow 00{:}50{:}46.790$  This was the program developed
- NOTE Confidence: 0.815990964416667
- $00:50:46.790 \longrightarrow 00:50:49.913$  colorectal cancer at 66 and we
- NOTE Confidence: 0.815990964416667

 $00:50:49.913 \longrightarrow 00:50:52.451$  tested this son that also had

NOTE Confidence: 0.815990964416667

 $00:50:52.451 \rightarrow 00:50:54.792$  sorry also had the mutation.

NOTE Confidence: 0.815990964416667

 $00:50:54.792 \rightarrow 00:50:56.936$  But however, these individuals

NOTE Confidence: 0.815990964416667

 $00:50:56.936 \longrightarrow 00:50:59.080$  in the second generation,

NOTE Confidence: 0.815990964416667

 $00:50:59.080 \longrightarrow 00:51:00.736$  because they are in their 40s,

NOTE Confidence: 0.815990964416667

 $00:51:00.740 \longrightarrow 00:51:02.570$  they might have not been able

NOTE Confidence: 0.815990964416667

 $00:51:02.570 \longrightarrow 00:51:03.974$  to develop cancer yet.

NOTE Confidence: 0.815990964416667

 $00:51:03.974 \rightarrow 00:51:05.959$  So this this course aggregation

NOTE Confidence: 0.815990964416667

00:51:05.959 - 00:51:07.990 study was not definitive.

NOTE Confidence: 0.759642116333333

 $00:51:10.030 \longrightarrow 00:51:12.811$  So then we wanted to to test what was

NOTE Confidence: 0.759642116333333

 $00{:}51{:}12{.}811 \dashrightarrow 00{:}51{:}15{.}417$  the effect of having a heterozygous

NOTE Confidence: 0.759642116333333

 $00:51:15.417 \rightarrow 00:51:18.550$  loss of function barrier in intestines.

NOTE Confidence: 0.759642116333333

 $00{:}51{:}18.550 \dashrightarrow 00{:}51{:}21.820$  So to do that we went back to to our

NOTE Confidence: 0.759642116333333

 $00:51:21.918 \rightarrow 00:51:25.649$  contacts in Spain and we extracted cells,

NOTE Confidence: 0.759642116333333

 $00{:}51{:}25{.}650 \dashrightarrow 00{:}51{:}28{.}884$  extracted blood samples from the two of

NOTE Confidence: 0.759642116333333

 $00:51:28.884 \rightarrow 00:51:32.086$  these songs that I show you in family.

 $00:51:32.090 \longrightarrow 00:51:33.458$  That one was a carrier and

NOTE Confidence: 0.759642116333333

 $00:51:33.458 \longrightarrow 00:51:34.630$  the other one was not.

NOTE Confidence: 0.759642116333333

 $00:51:34.630 \longrightarrow 00:51:36.700$  And we extracted that RNA.

NOTE Confidence: 0.759642116333333

 $00:51:36.700 \rightarrow 00:51:39.794$  We did the red transcription and qPCR.

NOTE Confidence: 0.759642116333333

 $00:51:39.800 \rightarrow 00:51:43.458$  To show that actually the level of gene

NOTE Confidence: 0.759642116333333

 $00:51:43.458 \rightarrow 00:51:46.160$  expression was significantly lower in the in,

NOTE Confidence: 0.759642116333333

 $00{:}51{:}46.160 \dashrightarrow 00{:}51{:}50.059$  in the brother that had the mutation.

NOTE Confidence: 0.759642116333333

00:51:50.060 - 00:51:53.100 And to test the effect in the Warner,

NOTE Confidence: 0.759642116333333

 $00{:}51{:}53{.}100 \dashrightarrow 00{:}51{:}55{.}755$  we had to use a different approach because we

NOTE Confidence: 0.759642116333333

 $00:51:55.755 \rightarrow 00:51:58.097$  didn't have access to that family anymore.

NOTE Confidence: 0.759642116333333

 $00{:}51{:}58{.}100 \dashrightarrow 00{:}52{:}01{.}118$  But we were likely to acquire

NOTE Confidence: 0.759642116333333

 $00{:}52{:}01{.}120 \dashrightarrow 00{:}52{:}04{.}192$  Lymphoblastoid cell line from family that

NOTE Confidence: 0.759642116333333

 $00{:}52{:}04{.}192 \dashrightarrow 00{:}52{:}07{.}875$  had there were these one mutation and

NOTE Confidence: 0.759642116333333

 $00:52:07.875 \rightarrow 00:52:10.706$  heterozygosity and from a control also.

NOTE Confidence: 0.759642116333333

 $00{:}52{:}10.706 \dashrightarrow 00{:}52{:}12.182$  And this mutation is the one

 $00:52:12.182 \longrightarrow 00:52:13.539$  that the cell lines have.

NOTE Confidence: 0.759642116333333

 $00:52:13.540 \rightarrow 00:52:15.988$  And it's just like a loss of function

NOTE Confidence: 0.759642116333333

 $00{:}52{:}15{.}988 \dashrightarrow 00{:}52{:}17{.}841$  mutation just for an amino acids

NOTE Confidence: 0.759642116333333

 $00:52:17.841 \longrightarrow 00:52:19.605$  down the line from the actual.

NOTE Confidence: 0.759642116333333

 $00{:}52{:}19.610 \dashrightarrow 00{:}52{:}20.810$  Colorectal cancer mutation that

NOTE Confidence: 0.759642116333333

 $00:52:20.810 \longrightarrow 00:52:23.170$  we found in one of the patients.

NOTE Confidence: 0.759642116333333

 $00:52:23.170 \longrightarrow 00:52:23.986$  So we extracted.

NOTE Confidence: 0.759642116333333

 $00:52:23.986 \longrightarrow 00:52:25.074$  We grow the cells.

NOTE Confidence: 0.759642116333333

 $00{:}52{:}25{.}080 \dashrightarrow 00{:}52{:}28{.}455$  We extracted proteins and we show that

NOTE Confidence: 0.759642116333333

 $00{:}52{:}28{.}455 \dashrightarrow 00{:}52{:}31{.}407$  again that there is an effect on the

NOTE Confidence: 0.759642116333333

 $00{:}52{:}31{.}407 \dashrightarrow 00{:}52{:}33{.}607$  heterozygous and the protein expression.

NOTE Confidence: 0.759642116333333

 $00{:}52{:}33{.}610 \dashrightarrow 00{:}52{:}35{.}549$  So with these we show that when

NOTE Confidence: 0.759642116333333

 $00:52:35.549 \rightarrow 00:52:37.661$  there is a when these individuals

NOTE Confidence: 0.759642116333333

00:52:37.661 --> 00:52:40.079 have a heterozygous well as a

NOTE Confidence: 0.759642116333333

 $00:52:40.079 \longrightarrow 00:52:41.539$  function in these genes,

NOTE Confidence: 0.759642116333333

 $00:52:41.540 \rightarrow 00:52:44.075$  they actually have a downregulation

- NOTE Confidence: 0.759642116333333
- $00{:}52{:}44.075 \dashrightarrow 00{:}52{:}46.610$  of the gene and protein.
- NOTE Confidence: 0.759642116333333
- $00:52:46.610 \longrightarrow 00:52:48.787$  So then we were interested in knowing
- NOTE Confidence: 0.759642116333333
- $00:52:48.787 \rightarrow 00:52:51.009$  well if there is a downregulation,
- NOTE Confidence: 0.759642116333333
- $00:52:51.010 \rightarrow 00:52:53.030$  what's happening with the activity
- NOTE Confidence: 0.759642116333333
- $00:52:53.030 \longrightarrow 00:52:55.550$  on the activity of the genes,
- NOTE Confidence: 0.759642116333333
- $00:52:55.550 \longrightarrow 00:52:56.966$  and how is that?
- NOTE Confidence: 0.759642116333333
- $00:52:56.966 \rightarrow 00:52:59.670$  How are these sales managing DNA damage?
- NOTE Confidence: 0.759642116333333
- 00:52:59.670 --> 00:53:00.460 Because again,
- NOTE Confidence: 0.759642116333333
- $00{:}53{:}00{.}460 \dashrightarrow 00{:}53{:}03{.}225$  remember that these are DNA repair genes.
- NOTE Confidence: 0.759642116333333
- $00:53:03.230 \rightarrow 00:53:05.552$  So to do that we grow the cells and
- NOTE Confidence: 0.759642116333333
- $00{:}53{:}05{.}552 \dashrightarrow 00{:}53{:}08{.}129$  we perform a flow cytometry analysis
- NOTE Confidence: 0.759642116333333
- $00:53:08.130 \longrightarrow 00:53:10.695$  that was actually testing the
- NOTE Confidence: 0.759642116333333
- $00:53:10.695 \rightarrow 00:53:13.756$  quantity of forceful relation of the
- NOTE Confidence: 0.759642116333333
- $00:53:13.756 \rightarrow 00:53:15.990$  serene 139 residue of the history.
- NOTE Confidence: 0.759642116333333
- $00:53:15.990 \longrightarrow 00:53:19.270$  Age to ax as an indicator of the
- NOTE Confidence: 0.759642116333333

 $00:53:19.270 \rightarrow 00:53:22.580$  damage and DNA double strand breaks.

NOTE Confidence: 0.759642116333333

 $00{:}53{:}22{.}580 \dashrightarrow 00{:}53{:}24{.}180$  So when we did that,

NOTE Confidence: 0.759642116333333

 $00:53:24.180 \longrightarrow 00:53:25.884$  we determined the phosphorylation

NOTE Confidence: 0.759642116333333

 $00:53:25.884 \longrightarrow 00:53:28.440$  at different time points and the

NOTE Confidence: 0.759642116333333

 $00:53:28.512 \rightarrow 00:53:30.542$  black are the wild type cells and

NOTE Confidence: 0.759642116333333

 $00:53:30.542 \longrightarrow 00:53:32.905$  the and the and Gray are the the

NOTE Confidence: 0.759642116333333

 $00:53:32.905 \longrightarrow 00:53:34.783$  ones with the headers I use,

NOTE Confidence: 0.759642116333333

 $00:53:34.783 \rightarrow 00:53:38.306$  so it's true that the first time

NOTE Confidence: 0.759642116333333

00:53:38.306 - 00:53:41.074 the first time point might be a delay

NOTE Confidence: 0.759642116333333

 $00:53:41.074 \rightarrow 00:53:44.089$  on the on on the phosphorylation we see

NOTE Confidence: 0.759642116333333

 $00:53:44.089 \rightarrow 00:53:46.822$  that on the other time points there

NOTE Confidence: 0.759642116333333

 $00:53:46.822 \rightarrow 00:53:49.780$  is a higher dose of the frustration and

NOTE Confidence: 0.759642116333333

 $00:53:49.780 \rightarrow 00:53:52.289$  therefore an indicator that these cells have.

NOTE Confidence: 0.759642116333333

 $00:53:52.290 \longrightarrow 00:53:55.074$  The higher DNA damage

NOTE Confidence: 0.759642116333333

 $00:53:55.074 \rightarrow 00:53:57.080$  and here as you can see,

NOTE Confidence: 0.759642116333333

 $00:53:57.080 \longrightarrow 00:53:58.788$  this is the difference

- NOTE Confidence: 0.759642116333333
- $00:53:58.788 \rightarrow 00:54:00.069$  between the heterozygote,
- NOTE Confidence: 0.759642116333333
- $00{:}54{:}00{.}070 \dashrightarrow 00{:}54{:}02{.}080$  the the heterozygous that has
- NOTE Confidence: 0.759642116333333
- $00:54:02.080 \rightarrow 00:54:07.010$  like a higher phosphorylation so.
- NOTE Confidence: 0.759642116333333
- $00:54:07.010 \rightarrow 00:54:09.770$  So right now we are also doing more
- NOTE Confidence: 0.759642116333333
- $00:54:09.770 \rightarrow 00:54:12.758$  analysis and we are testing for for example,
- NOTE Confidence: 0.759642116333333
- $00{:}54{:}12.760 \dashrightarrow 00{:}54{:}15.124$  for the effect of these variants
- NOTE Confidence: 0.759642116333333
- $00:54:15.124 \rightarrow 00:54:18.065$  in cell cycle because some of our
- NOTE Confidence: 0.759642116333333
- $00:54:18.065 \rightarrow 00:54:20.215$  preliminary data showing that maybe
- NOTE Confidence: 0.759642116333333
- $00:54:20.215 \rightarrow 00:54:23.196$  these cells are actually arrested in G1,
- NOTE Confidence: 0.759642116333333
- $00:54:23.200 \longrightarrow 00:54:27.136$  but we have not had this data yet.
- NOTE Confidence: 0.759642116333333
- $00:54:27.140 \longrightarrow 00:54:29.084$  So in conclusion from this aim
- NOTE Confidence: 0.759642116333333
- 00:54:29.084 --> 00:54:30.380 I we believe that
- NOTE Confidence: 0.69297737452
- 00:54:30.451 > 00:54:32.151 heterozygous loss of function
- NOTE Confidence: 0.69297737452
- 00:54:32.151 -> 00:54:34.276 variants in DNA repair genes
- NOTE Confidence: 0.69297737452
- $00{:}54{:}34{.}276$  -->  $00{:}54{:}36{.}596$  such as Warner and regular five,
- NOTE Confidence: 0.69297737452

 $00:54:36.600 \rightarrow 00:54:38.840$  could predispose to tumor development

NOTE Confidence: 0.69297737452

 $00:54:38.840 \rightarrow 00:54:41.080$  because they are enriched among

NOTE Confidence: 0.69297737452

00:54:41.150 - 00:54:43.230 the lines like cancer phenotype.

NOTE Confidence: 0.69297737452

 $00:54:43.230 \rightarrow 00:54:46.302$  They lead to gene down regulation

NOTE Confidence: 0.69297737452

 $00:54:46.302 \rightarrow 00:54:49.100$  and they increase DNA damage.

NOTE Confidence: 0.69297737452

 $00:54:49.100 \rightarrow 00:54:51.102$  So now turning it to the end

NOTE Confidence: 0.69297737452

 $00:54:51.102 \longrightarrow 00:54:53.069$  two at the somatic level.

NOTE Confidence: 0.69297737452

 $00:54:53.070 \longrightarrow 00:54:55.068$  Had to do develop these aim.

NOTE Confidence: 0.69297737452

 $00{:}54{:}55{.}070 \dashrightarrow 00{:}54{:}56{.}920$  We also included two different

NOTE Confidence: 0.69297737452

 $00{:}54{:}56{.}920 \dashrightarrow 00{:}54{:}58{.}770$  independent series of tumors that

NOTE Confidence: 0.69297737452

00:54:58.829 --> 00:55:00.473 mismatch repair deficient tumors

NOTE Confidence: 0.69297737452

00:55:00.473 - > 00:55:02.528 from the three different types,

NOTE Confidence: 0.69297737452

 $00{:}55{:}02{.}530 \dashrightarrow 00{:}55{:}05{.}450$  and we develop exam sequencing

NOTE Confidence: 0.69297737452

 $00:55:05.450 \longrightarrow 00:55:07.786$  to identify somatic variants

NOTE Confidence: 0.69297737452

 $00{:}55{:}07.786 \dashrightarrow 00{:}55{:}10.779$  and loss of hydrazoic events.

NOTE Confidence: 0.69297737452

 $00:55:10.780 \longrightarrow 00:55:12.260$  And with with this data,

 $00:55:12.260 \longrightarrow 00:55:14.096$  with this excellent data,

NOTE Confidence: 0.69297737452

 $00:55:14.096 \rightarrow 00:55:16.850$  we also were interested in defying

NOTE Confidence: 0.69297737452

 $00{:}55{:}16{.}935 \dashrightarrow 00{:}55{:}19{.}155$  the contribution of mutational

NOTE Confidence: 0.69297737452

 $00:55:19.155 \rightarrow 00:55:21.375$  signatures to these tumors.

NOTE Confidence: 0.69297737452

 $00{:}55{:}21{.}380 \dashrightarrow 00{:}55{:}23{.}715$  So mutational signatures are like

NOTE Confidence: 0.69297737452

 $00:55:23.715 \longrightarrow 00:55:26.617$  a fingerprint of the portrait

NOTE Confidence: 0.69297737452

 $00{:}55{:}26.617 \dashrightarrow 00{:}55{:}29.949$  of the mutations that the tumor has

NOTE Confidence: 0.69297737452

 $00:55:29.949 \longrightarrow 00:55:32.715$  acquired over the development of the

NOTE Confidence: 0.69297737452

 $00{:}55{:}32.715 \dashrightarrow 00{:}55{:}35.625$  tumor and they some of them are well

NOTE Confidence: 0.69297737452

 $00{:}55{:}35{.}625 \dashrightarrow 00{:}55{:}37{.}460$  established and they are associated to,

NOTE Confidence: 0.69297737452

 $00:55:37.460 \longrightarrow 00:55:38.246$  for example,

NOTE Confidence: 0.69297737452

 $00{:}55{:}38{.}246 \dashrightarrow 00{:}55{:}40{.}604$  exposure to carcinogens and other ones.

NOTE Confidence: 0.69297737452

 $00:55:40.610 \rightarrow 00:55:43.306$  Associated like in the case of the mismatch,

NOTE Confidence: 0.69297737452

00:55:43.310 --> 00:55:46.684 repair to deficiency on DNA repair pathways.

NOTE Confidence: 0.69297737452

 $00{:}55{:}46.690 \dashrightarrow 00{:}55{:}50.547$  So they the these are the six

 $00:55:50.550 \rightarrow 00:55:51.806$  current well established signatures

NOTE Confidence: 0.69297737452

 $00{:}55{:}51{.}806 \dashrightarrow 00{:}55{:}53{.}376$  that are associated with deficiency

NOTE Confidence: 0.69297737452

 $00:55:53.376 \longrightarrow 00:55:54.588$  of the mismatch repair.

NOTE Confidence: 0.69297737452

 $00:55:54.590 \longrightarrow 00:55:56.570$  So when these tumors have,

NOTE Confidence: 0.69297737452

 $00{:}55{:}56{.}570 \dashrightarrow 00{:}55{:}58{.}572$  when the tumors have deficiency and you

NOTE Confidence: 0.69297737452

 $00:55:58.572 \dashrightarrow 00:56:00.629$  analyze the the mutational signatures,

NOTE Confidence: 0.69297737452

 $00:56:00.630 \longrightarrow 00:56:02.990$  you can see this one so so we

NOTE Confidence: 0.69297737452

 $00:56:02.990 \longrightarrow 00:56:04.819$  were interested in knowing what

NOTE Confidence: 0.69297737452

 $00{:}56{:}04.819 \dashrightarrow 00{:}56{:}06.759$  was the contribution of these

NOTE Confidence: 0.69297737452

 $00:56:06.759 \rightarrow 00:56:08.849$  signatures to each of the tumors.

NOTE Confidence: 0.69297737452

 $00:56:08.850 \longrightarrow 00:56:10.634$  So let me explain.

NOTE Confidence: 0.69297737452

 $00:56:10.634 \rightarrow 00:56:12.864$  So this colorful graph here.

NOTE Confidence: 0.69297737452

 $00{:}56{:}12.870 \dashrightarrow 00{:}56{:}15.042$  So we first read identified what

NOTE Confidence: 0.69297737452

 $00:56:15.042 \rightarrow 00:56:16.850$  were the mutational signatures that

NOTE Confidence: 0.69297737452

 $00:56:16.850 \rightarrow 00:56:18.644$  were contributing the most to each

NOTE Confidence: 0.69297737452

 $00:56:18.644 \rightarrow 00:56:20.887$  of the tumor and then we perform

 $00:56:20.887 \rightarrow 00:56:22.819$  clustering to see whether the groups

NOTE Confidence: 0.69297737452

 $00:56:22.820 \longrightarrow 00:56:26.270$  of whether the tumors that have

NOTE Confidence: 0.69297737452

 $00{:}56{:}26{.}270 \dashrightarrow 00{:}56{:}29{.}280$  a similar contribution of those.

NOTE Confidence: 0.69297737452

 $00:56:29.280 \longrightarrow 00:56:33.016$  So here each each row is 1 tumor

NOTE Confidence: 0.69297737452

 $00{:}56{:}33.016 \dashrightarrow 00{:}56{:}35.174$  and each column is rotational.

NOTE Confidence: 0.69297737452

 $00:56:35.174 \longrightarrow 00:56:37.214$  It's a contribution of to

NOTE Confidence: 0.69297737452

 $00:56:37.214 \longrightarrow 00:56:38.820$  the mutational signatures,

NOTE Confidence: 0.69297737452

 $00:56:38.820 \rightarrow 00:56:42.036$  and here we are also having the phenotypes.

NOTE Confidence: 0.69297737452

 $00{:}56{:}42.040 \dashrightarrow 00{:}56{:}44.936$  So in here you can see the tumor

NOTE Confidence: 0.69297737452

 $00:56:44.936 \rightarrow 00:56:47.790$  is linch light lynch or the MSI?

NOTE Confidence: 0.69297737452

 $00:56:47.790 \longrightarrow 00:56:48.131$  Isolated.

NOTE Confidence: 0.69297737452

00:56:48.131 $\operatorname{-->}$ 00:56:50.859 And then in the last column here we

NOTE Confidence: 0.69297737452

 $00:56:50.859 \rightarrow 00:56:53.445$  are showing that which is the protein

NOTE Confidence: 0.69297737452

 $00{:}56{:}53.445 \dashrightarrow 00{:}56{:}55.800$  that each of these tumors have.

NOTE Confidence: 0.69297737452

 $00:56:55.800 \longrightarrow 00:56:57.436$  Most of the expression.

 $00:56:57.436 \rightarrow 00:56:59.890$  So when we perform this analysis,

NOTE Confidence: 0.69297737452

 $00{:}56{:}59{.}890 \dashrightarrow 00{:}57{:}02{.}634$  you can see with identified 2 of the

NOTE Confidence: 0.69297737452

 $00{:}57{:}02.640$  -->  $00{:}57{:}05.390$  that mutational signatures based on NOTE Confidence: 0.69297737452

 $00:57:05.390 \longrightarrow 00:57:09.684$  the the contribution of SBS 26 and 15,

NOTE Confidence: 0.69297737452

 $00:57:09.684 \rightarrow 00:57:11.539$  which are very well established.

NOTE Confidence: 0.69297737452

 $00{:}57{:}11{.}540$  -->  $00{:}57{:}13{.}284$  Mutational signatures associated with NOTE Confidence: 0.69297737452

 $00{:}57{:}13.284 \dashrightarrow 00{:}57{:}15.464$  deficiency of the mismatch repair

NOTE Confidence: 0.69297737452

 $00{:}57{:}15{.}470 \dashrightarrow 00{:}57{:}17{.}100$  identified first the two clusters

NOTE Confidence: 0.69297737452

 $00{:}57{:}17{.}100 \dashrightarrow 00{:}57{:}19{.}370$  that are in breach with the Lynch.

NOTE Confidence: 0.69297737452

 $00:57:19.370 \longrightarrow 00:57:20.381$  And the lynch,

NOTE Confidence: 0.69297737452

 $00{:}57{:}20{.}381 \dashrightarrow 00{:}57{:}22{.}740$  like and then we then defied this

NOTE Confidence: 0.69297737452

 $00{:}57{:}22.812 \dashrightarrow 00{:}57{:}25.212$  cluster that has a higher contribution

NOTE Confidence: 0.69297737452

 $00{:}57{:}25{.}212 \dashrightarrow 00{:}57{:}27{.}729$  of the tumors that are missing.

NOTE Confidence: 0.69297737452

 $00:57:27.730 \longrightarrow 00:57:29.240$  MSI,

NOTE Confidence: 0.69297737452

00:57:29.240 --> 00:57:32.260 MSI dated.

NOTE Confidence: 0.69297737452

 $00:57:32.260 \longrightarrow 00:57:35.270$  So here I'm I'm showing you the

- NOTE Confidence: 0.69297737452
- $00{:}57{:}35{.}270 \dashrightarrow 00{:}57{:}36{.}500$  different features associated
- NOTE Confidence: 0.69297737452
- 00:57:36.500 -> 00:57:38.900 with each of the the clusters,
- NOTE Confidence: 0.69297737452
- $00{:}57{:}38{.}900 \dashrightarrow 00{:}57{:}40{.}276$  and as I mentioned,
- NOTE Confidence: 0.69297737452
- $00{:}57{:}40.276 \dashrightarrow 00{:}57{:}42.873$  cluster two is enriched with MSI dated
- NOTE Confidence: 0.69297737452
- $00{:}57{:}42.873 \dashrightarrow 00{:}57{:}46.031$  and also this cluster has specific
- NOTE Confidence: 0.69297737452
- $00{:}57{:}46{.}031 \dashrightarrow 00{:}57{:}48{.}486$  clinical features that are well
- NOTE Confidence: 0.69297737452
- $00:57:48.486 \rightarrow 00:57:51.259$  established with this type of tumors,
- NOTE Confidence: 0.69297737452
- $00:57:51.260 \rightarrow 00:57:53.672$  which are that they develop preliminarily
- NOTE Confidence: 0.69297737452
- $00{:}57{:}53.672 \dashrightarrow 00{:}57{:}55.973$  and female patients at an older
- NOTE Confidence: 0.69297737452
- $00{:}57{:}55{.}973 \dashrightarrow 00{:}57{:}57{.}857$  age and that they are associated
- NOTE Confidence: 0.69297737452
- $00:57:57.857 \longrightarrow 00:57:59.870$  with the bright side location.
- NOTE Confidence: 0.764589175
- $00:58:01.910 \longrightarrow 00:58:03.198$  So as a molecularly,
- NOTE Confidence: 0.764589175
- $00:58:03.198 \longrightarrow 00:58:05.130$  as I as I explained you,
- NOTE Confidence: 0.764589175
- $00{:}58{:}05{.}130 \dashrightarrow 00{:}58{:}07{.}435$  this cluster is associated with
- NOTE Confidence: 0.764589175
- $00{:}58{:}07{.}435 \dashrightarrow 00{:}58{:}10{.}212$  thousand expression of mutl and mainly
- NOTE Confidence: 0.764589175

 $00:58:10.212 \rightarrow 00:58:12.570$  due to the manipulation of image

NOTE Confidence: 0.764589175

 $00{:}58{:}12{.}570 \dashrightarrow 00{:}58{:}15{.}790$  one and and then there's tumors.

NOTE Confidence: 0.764589175

 $00:58:15.790 \longrightarrow 00:58:17.560$  They also have the higher

NOTE Confidence: 0.764589175

00:58:17.560 - 00:58:19.330 number of frames if mutations,

NOTE Confidence: 0.764589175

 $00:58:19.330 \longrightarrow 00:58:22.095$  even though there is no difference in

NOTE Confidence: 0.764589175

 $00:58:22.095 \rightarrow 00:58:24.230$  tumor purity that could be affecting this.

NOTE Confidence: 0.764589175

 $00{:}58{:}24{.}230 \dashrightarrow 00{:}58{:}25{.}658$  But we didn't see that there

NOTE Confidence: 0.764589175

00:58:25.658 - 00:58:26.610 was a significant difference,

NOTE Confidence: 0.764589175

 $00{:}58{:}26{.}610 \dashrightarrow 00{:}58{:}28{.}164$  and they don't have a significant

NOTE Confidence: 0.764589175

 $00:58:28.164 \rightarrow 00:58:29.430$  difference in their own TMB.

NOTE Confidence: 0.764589175

 $00{:}58{:}29{.}430 \dashrightarrow 00{:}58{:}31{.}350$  So to like two more.

NOTE Confidence: 0.764589175

00:58:31.350 --> 00:58:32.100 Additional burden,

NOTE Confidence: 0.764589175

 $00:58:32.100 \rightarrow 00:58:34.350$  so it's specifically to the friendships

NOTE Confidence: 0.764589175

 $00:58:34.350 \rightarrow 00:58:36.498$  and what this suggests is that the

NOTE Confidence: 0.764589175

 $00:58:36.498 \longrightarrow 00:58:38.350$  the the tumors in this cluster.

NOTE Confidence: 0.764589175

 $00:58:38.350 \longrightarrow 00:58:40.140$  They actually have the higher

 $00:58:40.140 \rightarrow 00:58:41.930$  level of Microsoft the instability.

NOTE Confidence: 0.84446865875

 $00:58:43.970 \longrightarrow 00:58:46.007$  So one of the results of having

NOTE Confidence: 0.84446865875

 $00{:}58{:}46.007 \dashrightarrow 00{:}58{:}47.745$  a higher level of microsatellite

NOTE Confidence: 0.84446865875

 $00:58:47.745 \longrightarrow 00:58:50.139$  instability could be that these tumors

NOTE Confidence: 0.84446865875

 $00{:}58{:}50{.}139 \dashrightarrow 00{:}58{:}52{.}708$  have a different new antigen load,

NOTE Confidence: 0.84446865875

 $00{:}58{:}52{.}710 \dashrightarrow 00{:}58{:}55{.}560$  so new antigens are these peptides

NOTE Confidence: 0.84446865875

 $00{:}58{:}55{.}560 \dashrightarrow 00{:}58{:}57{.}846$  that are generated after somatic

NOTE Confidence: 0.84446865875

 $00:58:57.846 \longrightarrow 00:58:59.986$  mutations arise in the tumor.

NOTE Confidence: 0.84446865875

 $00{:}58{:}59{.}990 \dashrightarrow 00{:}59{:}01{.}190$  And as you can see here,

NOTE Confidence: 0.84446865875

 $00{:}59{:}01{.}190 \dashrightarrow 00{:}59{:}02{.}966$  you can see that the normal protein and

NOTE Confidence: 0.84446865875

 $00:59:02.966 \rightarrow 00:59:05.020$  this is a missense mutation in the tumor,

NOTE Confidence: 0.84446865875

 $00{:}59{:}05{.}020 \dashrightarrow 00{:}59{:}07{.}236$  so this is going to be 1 amino

NOTE Confidence: 0.84446865875

 $00{:}59{:}07{.}236 \dashrightarrow 00{:}59{:}08{.}718$  acid different from the self.

NOTE Confidence: 0.84446865875

 $00{:}59{:}08.720 \dashrightarrow 00{:}59{:}10.616$  The regular normal protein,

NOTE Confidence: 0.84446865875

 $00{:}59{:}10.616$  -->  $00{:}59{:}14.564$  but no antigens that are that are there.

- $00:59:14.564 \longrightarrow 00:59:16.220$  Develop from frame.
- NOTE Confidence: 0.84446865875
- 00:59:16.220 --> 00:59:18.540 Frameshift mutations are significantly
- NOTE Confidence: 0.84446865875
- $00{:}59{:}18.540 \dashrightarrow 00{:}59{:}21.440$  different from the normal because
- NOTE Confidence: 0.84446865875
- $00:59:21.440 \longrightarrow 00:59:25.340$  they introduce a lot of well.
- NOTE Confidence: 0.84446865875
- $00{:}59{:}25{.}340 \dashrightarrow 00{:}59{:}26{.}990$  Insertions and deletions.
- NOTE Confidence: 0.84446865875
- $00{:}59{:}26{.}990 \dashrightarrow 00{:}59{:}28{.}640$  So these proteins.
- NOTE Confidence: 0.84446865875
- $00:59:28.640 \rightarrow 00:59:30.580$  These peptides are significantly
- NOTE Confidence: 0.84446865875
- $00:59:30.580 \rightarrow 00:59:32.035$  different from cells,
- NOTE Confidence: 0.84446865875
- $00:59:32.040 \rightarrow 00:59:34.830$  and these new antigens which represented
- NOTE Confidence: 0.84446865875
- $00:59:34.830 \rightarrow 00:59:38.460$  here by this dot are presented from
- NOTE Confidence: 0.84446865875
- $00:59:38.460 \rightarrow 00:59:43.420$  through the HLA 1 receptor to the TCR.
- NOTE Confidence: 0.84446865875
- $00:59:43.420 \longrightarrow 00:59:45.100$  To the T cell receptors,
- NOTE Confidence: 0.84446865875
- $00:59:45.100 \rightarrow 00:59:47.340$  and this is obviously a very simplified
- NOTE Confidence: 0.84446865875
- $00{:}59{:}47{.}340 \dashrightarrow 00{:}59{:}48{.}920$  version of what's happening,
- NOTE Confidence: 0.84446865875
- $00:59:48.920 \longrightarrow 00:59:52.359$  but then when this is when when this
- NOTE Confidence: 0.84446865875
- $00:59:52.359 \rightarrow 00:59:55.740$  is happening then the T cells identify

- NOTE Confidence: 0.84446865875
- $00:59:55.740 \longrightarrow 00:59:59.577$  the tumor cells as as non self,

 $00:59:59.577 \rightarrow 01:00:02.372$  and then they're going to

NOTE Confidence: 0.84446865875

 $01:00:02.372 \longrightarrow 01:00:05.480$  start the immune response.

NOTE Confidence: 0.84446865875

 $01{:}00{:}05{.}480 \dashrightarrow 01{:}00{:}08{.}664$  So we wanted to see how these new

NOTE Confidence: 0.84446865875

 $01:00:08.664 \rightarrow 01:00:11.707$  antigens and the direction of the HLA.

NOTE Confidence: 0.84446865875

 $01:00:11.710 \longrightarrow 01:00:13.380$  Image of the patient were

NOTE Confidence: 0.84446865875

 $01{:}00{:}13.380 \dashrightarrow 01{:}00{:}15.050$  occurring based on the different

NOTE Confidence: 0.84446865875

 $01:00:15.109 \longrightarrow 01:00:16.779$  clusters that we are defined.

NOTE Confidence: 0.84446865875

 $01:00:16.780 \longrightarrow 01:00:20.924$  So to do that we use several

NOTE Confidence: 0.84446865875

 $01:00:20.924 \rightarrow 01:00:21.978$  bioinformatics pipelines.

NOTE Confidence: 0.84446865875

01:00:21.978 --> 01:00:24.726 We use Poly solver to predict

NOTE Confidence: 0.84446865875

01:00:24.726 $\operatorname{-->}$ 01:00:28.061 the HLA one alleles that we know

NOTE Confidence: 0.84446865875

 $01:00:28.061 \rightarrow 01:00:30.863$  that there's three of them using

NOTE Confidence: 0.84446865875

01:00:30.955 --> 01:00:33.600 the germline XM sequence data.

NOTE Confidence: 0.84446865875

 $01:00:33.600 \longrightarrow 01:00:36.301$  Then we use unaware tool to

- $01:00:36.301 \longrightarrow 01:00:38.706$  annotate all the mutations that
- NOTE Confidence: 0.84446865875
- $01:00:38.706 \longrightarrow 01:00:41.678$  we had identified in the in the.
- NOTE Confidence: 0.84446865875
- $01:00:41.680 \rightarrow 01:00:43.300$  More excellent sequencing and
- NOTE Confidence: 0.84446865875
- $01:00:43.300 \longrightarrow 01:00:44.920$  then we use net,
- NOTE Confidence: 0.84446865875
- $01:00:44.920 \longrightarrow 01:00:45.621$  MCA,
- NOTE Confidence: 0.84446865875
- $01:00:45.621 \rightarrow 01:00:49.126$  MHC pan that actually identifies
- NOTE Confidence: 0.84446865875
- $01:00:49.130 \longrightarrow 01:00:50.609$  what are what.
- NOTE Confidence: 0.84446865875
- $01{:}00{:}50.609 \dashrightarrow 01{:}00{:}53.074$  What are the interactions between
- NOTE Confidence: 0.84446865875
- $01{:}00{:}53.074 \dashrightarrow 01{:}00{:}56.610$  the HLA's and the new antigens?
- NOTE Confidence: 0.84446865875
- $01:00:56.610 \rightarrow 01:00:57.982$  And then we took it one step
- NOTE Confidence: 0.84446865875
- $01:00:57.982 \longrightarrow 01:00:59.348$  further and we use narrow pred.
- NOTE Confidence: 0.84446865875
- $01:00:59.350 \longrightarrow 01:01:02.890$  5 that actually this algorithm
- NOTE Confidence: 0.84446865875
- $01{:}01{:}02{.}890 \dashrightarrow 01{:}01{:}04{.}610$  computes the recognition potential.
- NOTE Confidence: 0.84446865875
- $01{:}01{:}04{.}610 \dashrightarrow 01{:}01{:}08{.}678$  So what it does is it provides a likelihood
- NOTE Confidence: 0.84446865875
- $01:01:08.678 \rightarrow 01:01:11.954$  that this interaction is going to occur.
- NOTE Confidence: 0.84446865875
- $01:01:11.960 \rightarrow 01:01:14.976$  And it's based on on the immune epitope.

- NOTE Confidence: 0.84446865875
- 01:01:14.980 --> 01:01:16.460 It's it's.
- NOTE Confidence: 0.84446865875
- $01:01:16.460 \longrightarrow 01:01:18.880$  It's this prediction is based
- NOTE Confidence: 0.84446865875
- 01:01:18.880 --> 01:01:20.980 on the TCR receptor rapporteur,
- NOTE Confidence: 0.84446865875
- $01{:}01{:}20{.}980 \dashrightarrow 01{:}01{:}24{.}828$  that it's that it's.
- NOTE Confidence: 0.84446865875
- $01{:}01{:}24.830 \dashrightarrow 01{:}01{:}27.305$  That he's present in the
- NOTE Confidence: 0.84446865875
- 01:01:27.305 01:01:28.790 immune epitope database.
- NOTE Confidence: 0.84446865875
- $01:01:28.790 \longrightarrow 01:01:33.870$  So with that we took this likelihood
- NOTE Confidence: 0.84446865875
- 01:01:33.870 --> 01:01:36.470 and this recognition potential,
- NOTE Confidence: 0.84446865875
- $01:01:36.470 \longrightarrow 01:01:37.858$  and we score them,
- NOTE Confidence: 0.84446865875
- $01:01:37.858 \longrightarrow 01:01:39.940$  and we identified the ones that
- NOTE Confidence: 0.84446865875
- $01:01:40.012 \longrightarrow 01:01:42.250$  were at the highest 10% tile and
- NOTE Confidence: 0.84446865875
- $01:01:42.250 \longrightarrow 01:01:44.810$  the ones that were at the lower 10%.
- NOTE Confidence: 0.84446865875
- $01{:}01{:}44.810 \dashrightarrow 01{:}01{:}48.743$  So we assume that if there is no selection,
- NOTE Confidence: 0.84446865875
- 01:01:48.750 $\operatorname{-->}$ 01:01:51.070 then the these interactions in
- NOTE Confidence: 0.84446865875
- $01{:}01{:}51{.}070 \dashrightarrow 01{:}01{:}54{.}470$  the temple in the top percentile.
- NOTE Confidence: 0.84446865875

 $01:01:54.470 \rightarrow 01:01:57.116$  Between the new antigens and the HLA,

NOTE Confidence: 0.84446865875

 $01{:}01{:}57{.}120 \dashrightarrow 01{:}01{:}59{.}490$  one should be the distribution of

NOTE Confidence: 0.84446865875

 $01{:}01{:}59{.}490 \dashrightarrow 01{:}02{:}01{.}998$  these alleles should be similar to

NOTE Confidence: 0.84446865875

 $01:02:01.998 \longrightarrow 01:02:04.128$  the distribution of the patients

NOTE Confidence: 0.84446865875

 $01{:}02{:}04{.}130 \dashrightarrow 01{:}02{:}06{.}488$  and the little frequency in the

NOTE Confidence: 0.84446865875

 $01:02:06.488 \longrightarrow 01:02:07.274$  patient population.

NOTE Confidence: 0.84446865875

 $01:02:07.280 \longrightarrow 01:02:11.102$  So to test this hypothesis we we

NOTE Confidence: 0.84446865875

 $01:02:11.102 \longrightarrow 01:02:13.886$  compare the actual frequency of the

NOTE Confidence: 0.84446865875

 $01:02:13.886 \rightarrow 01:02:16.178$  alleles in the patient population for NOTE Confidence: 0.84446865875

01:02:16.178  $-\!>$  01:02:18.708 each of the different clusters and

NOTE Confidence: 0.84446865875

01:02:18.708 --> 01:02:20.783 the frequency and the distribution

NOTE Confidence: 0.84446865875

 $01:02:20.850 \longrightarrow 01:02:22.985$  of the alleles in the ones that

NOTE Confidence: 0.84446865875

 $01:02:22.985 \rightarrow 01:02:25.199$  are selected as having the higher.

NOTE Confidence: 0.84446865875

 $01:02:25.199 \longrightarrow 01:02:27.364$  Likely for the recognition and

NOTE Confidence: 0.84446865875

 $01:02:27.364 \longrightarrow 01:02:28.230$  what we

NOTE Confidence: 0.796941060842105

 $01{:}02{:}28{.}313 \dashrightarrow 01{:}02{:}31{.}199$  identified is that actually there was

 $01:02:31.199 \longrightarrow 01:02:33.931$  one specific allele B702 that were

NOTE Confidence: 0.796941060842105

01:02:33.931 $\operatorname{-->}$ 01:02:36.806 significantly in breach in this in

NOTE Confidence: 0.796941060842105

 $01:02:36.806 \rightarrow 01:02:40.486$  the top 10% recognition potential,

NOTE Confidence: 0.796941060842105

 $01:02:40.490 \longrightarrow 01:02:43.058$  which that was not happening in

NOTE Confidence: 0.796941060842105

 $01{:}02{:}43.058 \dashrightarrow 01{:}02{:}46.290$  the lower set of of interactions.

NOTE Confidence: 0.796941060842105

 $01:02:46.290 \longrightarrow 01:02:49.594$  So we think that the specific actually

NOTE Confidence: 0.796941060842105

 $01{:}02{:}49{.}594 \dashrightarrow 01{:}02{:}52{.}961$  wanna leaves like the B702 could promote

NOTE Confidence: 0.796941060842105

 $01:02:52.961 \rightarrow 01:02:55.109$  stronger immune immune response.

NOTE Confidence: 0.796941060842105

 $01{:}02{:}55{.}110 \dashrightarrow 01{:}02{:}57{.}646$  And these tumors that are the ones with

NOTE Confidence: 0.796941060842105

 $01:02:57.646 \rightarrow 01:03:00.059$  the higher microsatellite instability.

NOTE Confidence: 0.796941060842105

 $01:03:00.060 \rightarrow 01:03:02.348$  And we believe that these down the line

NOTE Confidence: 0.796941060842105

 $01{:}03{:}02{.}348 \dashrightarrow 01{:}03{:}05{.}808$  could be affecting the immune response

NOTE Confidence: 0.796941060842105

 $01{:}03{:}05{.}808 \dashrightarrow 01{:}03{:}10{.}790$  of these tumors to and how to

NOTE Confidence: 0.796941060842105

 $01{:}03{:}10.790 \dashrightarrow 01{:}03{:}13.038$  immune immune checkpoint inhibitors.

NOTE Confidence: 0.796941060842105

 $01{:}03{:}13.040 \dashrightarrow 01{:}03{:}16.407$  So obviously this is the the beginning

 $01:03:16.407 \longrightarrow 01:03:19.146$  of like expanding this work in

NOTE Confidence: 0.796941060842105

 $01:03:19.146 \rightarrow 01:03:21.967$  the area of immune response by the

NOTE Confidence: 0.796941060842105

 $01:03:22.061 \rightarrow 01:03:25.237$  immune checkpoint inhibitor response.

NOTE Confidence: 0.796941060842105

 $01:03:25.240 \longrightarrow 01:03:26.317$  So in conclusion,

NOTE Confidence: 0.796941060842105

 $01{:}03{:}26{.}317 \dashrightarrow 01{:}03{:}28{.}471$  for him two molecular differences between

NOTE Confidence: 0.796941060842105

 $01{:}03{:}28{.}471 \dashrightarrow 01{:}03{:}31{.}225$  the three different types of mismatch repair,

NOTE Confidence: 0.796941060842105

01:03:31.230 $\operatorname{-->}$ 01:03:34.482 deficient tumors could have a direct

NOTE Confidence: 0.796941060842105

 $01:03:34.482 \rightarrow 01:03:37.450$  implication and immune response specific.

NOTE Confidence: 0.796941060842105

 $01{:}03{:}37{.}450 \dashrightarrow 01{:}03{:}39{.}956$  One else could be driving the presentation

NOTE Confidence: 0.796941060842105

 $01:03:39.956 \longrightarrow 01:03:41.919$  of neoantigens among mismatch repair

NOTE Confidence: 0.796941060842105

 $01{:}03{:}41{.}919 \dashrightarrow 01{:}03{:}43{.}994$  deficient tumors with the highest

NOTE Confidence: 0.796941060842105

 $01:03:43.994 \rightarrow 01:03:45.980$  level of microsatellite instability.

NOTE Confidence: 0.796941060842105

01:03:45.980 --> 01:03:48.320 We probably specially this work,

NOTE Confidence: 0.796941060842105

 $01{:}03{:}48.320 \dashrightarrow 01{:}03{:}50.816$  so overall the take home message is that

NOTE Confidence: 0.796941060842105

 $01{:}03{:}50{.}816 \dashrightarrow 01{:}03{:}53{.}313$  our studies show that there's novel

NOTE Confidence: 0.796941060842105

 $01:03:53.313 \rightarrow 01:03:55.117$  molecular heterogeneity among these.

 $01{:}03{:}55{.}120 \dashrightarrow 01{:}03{:}57{.}410$  Under the efficient tumors and

NOTE Confidence: 0.796941060842105

 $01:03:57.410 \longrightarrow 01:03:59.242$  that understanding the clinical

NOTE Confidence: 0.796941060842105

 $01:03:59.242 \rightarrow 01:04:01.268$  pathological features associated with

NOTE Confidence: 0.796941060842105

 $01:04:01.268 \rightarrow 01:04:03.272$  this heterogeneous heterogeneity is

NOTE Confidence: 0.796941060842105

01:04:03.272 --> 01:04:05.620 essential to accurate diagnosis and

NOTE Confidence: 0.796941060842105

 $01{:}04{:}05.620 \dashrightarrow 01{:}04{:}07.575$  prediction of treatment response in

NOTE Confidence: 0.796941060842105

 $01:04:07.575 \rightarrow 01:04:10.050$  the setting of personalized medicine.

NOTE Confidence: 0.796941060842105

 $01:04:10.050 \rightarrow 01:04:12.650$  And our future directions.

NOTE Confidence: 0.796941060842105

 $01{:}04{:}12.650 \dashrightarrow 01{:}04{:}14.785$  It's to understand the molecular

NOTE Confidence: 0.796941060842105

 $01{:}04{:}14.785 \dashrightarrow 01{:}04{:}16.920$  mechanism that associate trequel 5

NOTE Confidence: 0.796941060842105

01:04:16.987 --> 01:04:19.357 and Warner deficiency with this type

NOTE Confidence: 0.796941060842105

 $01:04:19.357 \rightarrow 01:04:21.419$  of tumors identify immune regulators

NOTE Confidence: 0.796941060842105

 $01{:}04{:}21{.}419$  -->  $01{:}04{:}23{.}903$  that determine response based on the

NOTE Confidence: 0.796941060842105

01:04:23.903 --> 01:04:26.602 type the specific type of mismatch

NOTE Confidence: 0.796941060842105

01:04:26.602 --> 01:04:27.570 repair deficiency,

 $01:04:27.570 \rightarrow 01:04:29.975$  and investigate also the treatment

NOTE Confidence: 0.796941060842105

01:04:29.975 --> 01:04:31.899 response to immune checkpoint

NOTE Confidence: 0.796941060842105

 $01:04:31.899 \longrightarrow 01:04:34.411$  inhibitors based on this type of

NOTE Confidence: 0.796941060842105

01:04:34.411 --> 01:04:35.590 mismatch repair deficiency.

NOTE Confidence: 0.796941060842105

01:04:35.590 --> 01:04:37.015 So with that,

NOTE Confidence: 0.796941060842105

01:04:37.015 --> 01:04:39.390 just acknowledge our funding sources

NOTE Confidence: 0.796941060842105

 $01{:}04{:}39{.}390 \dashrightarrow 01{:}04{:}41{.}856$  Martinek Albuch that is the first

NOTE Confidence: 0.796941060842105

01:04:41.856 --> 01:04:44.809 dog in my lab that has one done most

NOTE Confidence: 0.796941060842105

 $01{:}04{:}44{.}809 \dashrightarrow 01{:}04{:}46{.}969$  of the work and my collaborators

NOTE Confidence: 0.796941060842105

 $01:04:46.970 \longrightarrow 01:04:49.287$  in the US and also in Spain.

NOTE Confidence: 0.796941060842105

 $01{:}04{:}49{.}290 \dashrightarrow 01{:}04{:}51{.}874$  And I'll be happy to take any questions.

NOTE Confidence: 0.869126174

01:04:52.850 --> 01:04:55.170 Thank you very much Rosa.

NOTE Confidence: 0.869126174

 $01{:}04{:}55{.}170 \dashrightarrow 01{:}04{:}57{.}242$  A terrific work that's very interesting and

NOTE Confidence: 0.869126174

 $01{:}04{:}57{.}242 \dashrightarrow 01{:}05{:}00{.}048$  we do have a couple of questions in the chat,

NOTE Confidence: 0.869126174

 $01:05:00.050 \rightarrow 01:05:05.056$  so which hopefully I can read properly.

NOTE Confidence: 0.869126174

 $01:05:05.056 \rightarrow 01:05:08.014$  So the first is from Jeffrey
- NOTE Confidence: 0.869126174
- $01:05:08.014 \rightarrow 01:05:09.969$  Townsend and Jeff asks,

NOTE Confidence: 0.869126174

 $01{:}05{:}09{.}970 \dashrightarrow 01{:}05{:}13{.}590$  is the association of BRAF V600E

NOTE Confidence: 0.869126174

 $01:05:13.590 \rightarrow 01:05:16.990$  with MSH mutation purely mutational?

NOTE Confidence: 0.869126174

01:05:16.990 --> 01:05:19.517 Or is there some more complex biology

NOTE Confidence: 0.869126174

01:05:19.517 $\operatorname{-->}$ 01:05:22.322 to the association and he asks because

NOTE Confidence: 0.869126174

 $01{:}05{:}22.322 \dashrightarrow 01{:}05{:}23.970$  the trinucleotide signature in.

NOTE Confidence: 0.869126174

 $01{:}05{:}23.970 \dashrightarrow 01{:}05{:}26.658$  Used by MSH is especially likely to

NOTE Confidence: 0.869126174

 $01{:}05{:}26.658 \dashrightarrow 01{:}05{:}30.050$  make the B Rav 600 to E mutation. Yeah

NOTE Confidence: 0.64577244225

 $01{:}05{:}30.060 \dashrightarrow 01{:}05{:}33.300$  so so. The BRAF mutation in colon cancer

NOTE Confidence: 0.64577244225

 $01:05:33.300 \rightarrow 01:05:36.140$  is associated with the serrated pathway,

NOTE Confidence: 0.64577244225

 $01:05:36.140 \dashrightarrow 01:05:38.216$  so that's like the more biological.

NOTE Confidence: 0.64577244225

 $01:05:38.220 \longrightarrow 01:05:39.948$  It's not this type of tumors,

NOTE Confidence: 0.64577244225

 $01{:}05{:}39{.}950 \dashrightarrow 01{:}05{:}42{.}056$  but for the for the Ms,

NOTE Confidence: 0.64577244225

01:05:42.060 --> 01:05:44.280 I believe it's more like a

NOTE Confidence: 0.64577244225

 $01:05:44.280 \longrightarrow 01:05:45.314$  motivational association,

NOTE Confidence: 0.64577244225

 $01:05:45.314 \longrightarrow 01:05:48.933$  but the one that has been more

NOTE Confidence: 0.64577244225

 $01:05:48.933 \rightarrow 01:05:51.349$  described biologically is the one

NOTE Confidence: 0.64577244225

 $01:05:51.349 \rightarrow 01:05:54.073$  that the the servated pathway.

NOTE Confidence: 0.64577244225

 $01:05:54.080 \rightarrow 01:05:56.211$  Had tumors that they were writing.

NOTE Confidence: 0.64577244225

01:05:56.211 --> 01:05:57.864 Passwords are developing,

NOTE Confidence: 0.64577244225

 $01{:}05{:}57{.}864 \dashrightarrow 01{:}06{:}01{.}170$  but this is like more like.

NOTE Confidence: 0.64577244225

 $01{:}06{:}01{.}170 \dashrightarrow 01{:}06{:}03.475$  Mutational that we used to

NOTE Confidence: 0.64577244225

01:06:03.475 -> 01:06:05.319 mainly separate the sporadic

NOTE Confidence: 0.64577244225

 $01{:}06{:}05{.}319 \dashrightarrow 01{:}06{:}07{.}398$  from the hereditary ones.

NOTE Confidence: 0.831493464

 $01:06:09.130 \longrightarrow 01:06:10.444$  OK great thanks.

NOTE Confidence: 0.831493464

 $01{:}06{:}10.444 \dashrightarrow 01{:}06{:}13.072$  And then the next question is

NOTE Confidence: 0.831493464

01:06:13.072 --> 01:06:15.827 from Ryan Jensen and Ryan asks.

NOTE Confidence: 0.831493464

 $01{:}06{:}15.830 \dashrightarrow 01{:}06{:}18.623$  And one of the potential roles of

NOTE Confidence: 0.831493464

 $01{:}06{:}18.623 \dashrightarrow 01{:}06{:}21.918$  of REC QL 5 is to prevent aberrant

NOTE Confidence: 0.831493464

 $01:06:21.918 \rightarrow 01:06:24.350$  homologous recombination by displacing

NOTE Confidence: 0.831493464

 $01:06:24.350 \rightarrow 01:06:26.726$  RAD 51 off single stranded DNA.

- NOTE Confidence: 0.831493464
- $01:06:26.726 \longrightarrow 01:06:28.858$  And he wonders if in tumors from

NOTE Confidence: 0.831493464

01:06:28.858 --> 01:06:30.528 patients with loss of function,

NOTE Confidence: 0.831493464

 $01{:}06{:}30{.}530 \dashrightarrow 01{:}06{:}33{.}750$  mutations in REC queue do you see

NOTE Confidence: 0.831493464

 $01:06:33.750 \rightarrow 01:06:35.514$  increased chromosomal aberrations?

NOTE Confidence: 0.831493464

01:06:35.514 --> 01:06:37.470 Sister chromatid exchanges,

NOTE Confidence: 0.831493464

 $01{:}06{:}37{.}470 \dashrightarrow 01{:}06{:}40{.}480$  or perhaps increases in microsatellite

NOTE Confidence: 0.831493464

 $01:06:40.480 \longrightarrow 01:06:42.286$  contraction or expansion.

NOTE Confidence: 0.865207728333333

 $01:06:43.010 \rightarrow 01:06:45.702$  So all of these we have, we.

NOTE Confidence: 0.865207728333333

01:06:45.702 --> 01:06:50.420 There's so the the work done in Q L5

NOTE Confidence: 0.865207728333333

 $01{:}06{:}50{.}420 \dashrightarrow 01{:}06{:}53{.}280$  and colorectal cancer is not very vast.

NOTE Confidence: 0.865207728333333

 $01{:}06{:}53.280 \dashrightarrow 01{:}06{:}56.508$  So so right now what I can say is that

NOTE Confidence: 0.865207728333333

 $01{:}06{:}56{.}508 \dashrightarrow 01{:}06{:}59{.}721$  we we just engineer a cell line that is,

NOTE Confidence: 0.865207728333333

 $01{:}06{:}59{.}730 \dashrightarrow 01{:}07{:}00.838$  that has these mutations,

NOTE Confidence: 0.865207728333333

 $01{:}07{:}00.838 \dashrightarrow 01{:}07{:}03.058$  which rupees per so we are going to

NOTE Confidence: 0.865207728333333

 $01{:}07{:}03.058 \dashrightarrow 01{:}07{:}05.058$  have the cell lines that have like the

NOTE Confidence: 0.865207728333333

01:07:05.119 --> 01:07:07.357 heterozygous and homozygous and Val types.

NOTE Confidence: 0.865207728333333

 $01{:}07{:}07{.}360 \dashrightarrow 01{:}07{:}10{.}024$  So we are going to be testing these

NOTE Confidence: 0.865207728333333

 $01:07:10.024 \rightarrow 01:07:13.256$  kind of events that Brian is suggesting.

NOTE Confidence: 0.865207728333333

 $01{:}07{:}13.260 \dashrightarrow 01{:}07{:}14.886$  So I don't have that information

NOTE Confidence: 0.865207728333333

01:07:14.886 - 01:07:16.920 yet where I know that, for example,

NOTE Confidence: 0.865207728333333

 $01{:}07{:}16{.}920 \dashrightarrow 01{:}07{:}19{.}660$  for Frank L5 is that there there's been one.

NOTE Confidence: 0.865207728333333

01:07:19.660 --> 01:07:22.292 There was one old paper that was

NOTE Confidence: 0.865207728333333

 $01:07:22.292 \rightarrow 01:07:25.798$  showing that interestingly regular 5

NOTE Confidence: 0.865207728333333

01:07:25.798 --> 01:07:29.230 downregulation was identified in MSI tumors,

NOTE Confidence: 0.865207728333333

 $01{:}07{:}29{.}230 \dashrightarrow 01{:}07{:}32{.}438$  and so I think that there is more

NOTE Confidence: 0.865207728333333

 $01{:}07{:}32{.}438 \dashrightarrow 01{:}07{:}34{.}965$  than we can be learning about this

NOTE Confidence: 0.865207728333333

 $01:07:34.965 \longrightarrow 01:07:36.458$  and and I think that that's going

NOTE Confidence: 0.865207728333333

 $01{:}07{:}36.458 \dashrightarrow 01{:}07{:}38.147$  to be one of our like next steps.

NOTE Confidence: 0.729372912222222

 $01{:}07{:}39.670 \dashrightarrow 01{:}07{:}43.189$  Great thank you and I had one quick question.

NOTE Confidence: 0.729372912222222

 $01:07:43.190 \longrightarrow 01:07:44.594$  When you were going

NOTE Confidence: 0.729372912222222

 $01:07:44.594 \rightarrow 01:07:46.349$  through and looking at the.

NOTE Confidence: 0.729372912222222

 $01:07:46.350 \longrightarrow 01:07:48.546$  The the red queue and other

NOTE Confidence: 0.729372912222222

 $01:07:48.546 \rightarrow 01:07:51.109$  mutations in the Lynch like syndrome.

NOTE Confidence: 0.729372912222222

 $01{:}07{:}51{.}110 \dashrightarrow 01{:}07{:}53{.}789$  I didn't have a sense for for whether

NOTE Confidence: 0.729372912222222

 $01:07:53.789 \rightarrow 01:07:55.103$  it was clear whether that they're

NOTE Confidence: 0.729372912222222

 $01:07:55.103 \longrightarrow 01:07:56.590$  all loss of function mutations,

NOTE Confidence: 0.729372912222222

 $01{:}07{:}56.590 \dashrightarrow 01{:}07{:}59.518$  like for example the T31K in that one

NOTE Confidence: 0.729372912222222

 $01:07:59.518 \longrightarrow 01:08:02.668$  family is that is that some is that a is

NOTE Confidence: 0.790083059375

 $01{:}08{:}02.680 \dashrightarrow 01{:}08{:}05.200$  that one so that one was mutation that

NOTE Confidence: 0.790083059375

 $01:08:05.200 \dashrightarrow 01:08:07.847$  we found in the tumor of that patient.

NOTE Confidence: 0.790083059375

 $01:08:07.850 \longrightarrow 01:08:09.782$  We have not been able to

NOTE Confidence: 0.790083059375

 $01:08:09.782 \longrightarrow 01:08:11.070$  test the other individual.

NOTE Confidence: 0.790083059375

 $01{:}08{:}11{.}070 \dashrightarrow 01{:}08{:}12{.}775$  So the germline variants that

NOTE Confidence: 0.790083059375

 $01:08:12.775 \longrightarrow 01:08:14.900$  we are even defining in the

NOTE Confidence: 0.790083059375

 $01{:}08{:}14.900 \dashrightarrow 01{:}08{:}16.994$  germline are all loss of function.

NOTE Confidence: 0.790083059375

 $01{:}08{:}17{.}000 \dashrightarrow 01{:}08{:}19{.}920$  But we only have been able to test

NOTE Confidence: 0.790083059375

 $01:08:19.920 \longrightarrow 01:08:22.738$  1 tumor from these individuals.

NOTE Confidence: 0.790083059375

01:08:22.740 --> 01:08:24.525 I can tell you, not for AQL.

NOTE Confidence: 0.790083059375

 $01:08:24.530 \longrightarrow 01:08:26.922$  I know a lot of the data for

NOTE Confidence: 0.790083059375

 $01:08:26.922 \longrightarrow 01:08:30.107$  one not a lot few data from

NOTE Confidence: 0.790083059375

 $01{:}08{:}30{.}107 \dashrightarrow 01{:}08{:}31{.}604$  Warner mutation somatically.

NOTE Confidence: 0.790083059375

 $01:08:31.610 \longrightarrow 01:08:34.646$  There is the there identifying loss NOTE Confidence: 0.790083059375

01:08:34.646 --> 01:08:37.266 of function mutations and actually

NOTE Confidence: 0.790083059375

 $01{:}08{:}37.266 \dashrightarrow 01{:}08{:}40.302$  these tumors that have loss of

NOTE Confidence: 0.790083059375

 $01:08:40.302 \rightarrow 01:08:42.990$  function mutations in Werner they NOTE Confidence: 0.790083059375

 $01:08:42.990 \longrightarrow 01:08:45.453$  have a significantly higher number NOTE Confidence: 0.790083059375

 $01:08:45.453 \rightarrow 01:08:47.574$  of them in comparison to the ones NOTE Confidence: 0.790083059375

 $01:08:47.574 \rightarrow 01:08:49.490$  that don't have mutations there.

NOTE Confidence: 0.790083059375

01:08:49.490 --> 01:08:52.808 MSI. So again another kind of.

NOTE Confidence: 0.790083059375

 $01{:}08{:}52{.}810 \dashrightarrow 01{:}08{:}55{.}342$  Another clue that there have there

NOTE Confidence: 0.790083059375

 $01{:}08{:}55{.}342 \dashrightarrow 01{:}08{:}58{.}191$  might be some some association between

NOTE Confidence: 0.790083059375

 $01:08:58.191 \dashrightarrow 01:09:01.419$  deficiency in these genes and MSI.

- NOTE Confidence: 0.790083059375
- $01:09:01.420 \rightarrow 01:09:03.940$  However, association doesn't mean causality,
- NOTE Confidence: 0.790083059375
- $01{:}09{:}03{.}940 \dashrightarrow 01{:}09{:}05{.}536$  so this is what I think that
- NOTE Confidence: 0.790083059375
- $01:09:05.536 \longrightarrow 01:09:07.459$  is what we actually need to do.
- NOTE Confidence: 0.790083059375
- $01:09:07.460 \longrightarrow 01:09:08.970$  More research to figure out
- NOTE Confidence: 0.790083059375
- $01{:}09{:}08{.}970 \dashrightarrow 01{:}09{:}10{.}910$  these needs one or the other.
- NOTE Confidence: 0.804723313333333
- $01{:}09{:}12.290 \dashrightarrow 01{:}09{:}17.726$  Good, well I think it's been a great session.
- NOTE Confidence: 0.804723313333333
- $01:09:17.730 \longrightarrow 01:09:19.155$  And lots of good questions
- NOTE Confidence: 0.804723313333333
- $01:09:19.155 \longrightarrow 01:09:20.580$  and and two fantastic talks.
- NOTE Confidence: 0.804723313333333
- 01:09:20.580 --> 01:09:22.645 So I'd like to just to finish
- NOTE Confidence: 0.804723313333333
- $01:09:22.645 \longrightarrow 01:09:24.608$  by by thanking Luisa and Rosa.
- NOTE Confidence: 0.804723313333333
- 01:09:24.610 --> 01:09:26.500 Very much for really giving very
- NOTE Confidence: 0.804723313333333
- $01:09:26.500 \longrightarrow 01:09:27.760$  stimulating and exciting talks,
- NOTE Confidence: 0.804723313333333
- $01:09:27.760 \longrightarrow 01:09:30.250$  great grand rounds and thank
- NOTE Confidence: 0.804723313333333
- $01{:}09{:}30{.}250 \dashrightarrow 01{:}09{:}32{.}242$  you very much every body.
- NOTE Confidence: 0.804723313333333
- $01:09:32.250 \longrightarrow 01:09:34.828$  Thank you. By e by e by e.