WEBVTT

- NOTE duration:"00:45:56"
- NOTE recognizability:0.844
- NOTE language:en-us
- NOTE Confidence: 0.66406729
- 00:00:00.000 --> 00:00:02.432 I'm, I'm iron crop.
- NOTE Confidence: 0.66406729
- $00{:}00{:}02{.}432 \dashrightarrow 00{:}00{:}06{.}090$  I'm the CTO director here and it's
- NOTE Confidence: 0.66406729

00:00:06.090 --> 00:00:07.920 my pleasure to introduce David Rimm,

- NOTE Confidence: 0.66406729
- $00{:}00{:}07{.}920 \dashrightarrow 00{:}00{:}10{.}840$  who has many of you know is the Anthony Brady
- NOTE Confidence: 0.66406729
- 00:00:10.913 --> 00:00:13.577 Professor of Pathology and medicine here.
- NOTE Confidence: 0.66406729
- 00:00:13.580 --> 00:00:17.940 He is a Hopkins alum, did an MD PhD there,
- NOTE Confidence: 0.66406729
- $00:00:17.940 \longrightarrow 00:00:20.674$  then came here for for pathology residency
- NOTE Confidence: 0.66406729
- $00:00:20.674 \rightarrow 00:00:23.758$  and then did a psychopath fellowship
- NOTE Confidence: 0.66406729
- $00:00:23.758 \rightarrow 00:00:27.078$  at the Medical College of Virginia.
- NOTE Confidence: 0.66406729
- $00:00:27.080 \longrightarrow 00:00:29.050$  He's actually now been at
- NOTE Confidence: 0.66406729
- $00:00:29.050 \longrightarrow 00:00:31.020$  Yale for almost 30 years.
- NOTE Confidence: 0.66406729
- $00:00:31.020 \longrightarrow 00:00:31.950$  That's impressive.
- NOTE Confidence: 0.66406729
- $00:00:31.950 \rightarrow 00:00:34.740$  He's the director of the Pathology
- NOTE Confidence: 0.66406729

 $00:00:34.740 \longrightarrow 00:00:37.619$  tissue service here and serves as

NOTE Confidence: 0.66406729

00:00:37.619 --> 00:00:39.499 director of Translational Pathology.

NOTE Confidence: 0.66406729

00:00:39.500 --> 00:00:42.097 You know, I think David has been

NOTE Confidence: 0.66406729

 $00:00:42.097 \longrightarrow 00:00:43.520$  at the forefront of.

NOTE Confidence: 0.66406729

 $00{:}00{:}43.520 \dashrightarrow 00{:}00{:}46.500$  I guess I don't need to as in the

NOTE Confidence: 0.66406729

 $00:00:46.500 \rightarrow 00:00:48.860$  for efront of quantitative pathology NOTE Confidence: 0.66406729

00:00:48.860 --> 00:00:52.594 for for many years and he's well

NOTE Confidence: 0.66406729

 $00:00:52.594 \rightarrow 00:00:54.794$  known throughout the the, the.

NOTE Confidence: 0.66406729

 $00{:}00{:}54.794 \dashrightarrow 00{:}00{:}57.218$  The field for this he developed

NOTE Confidence: 0.66406729

 $00{:}00{:}57{.}218 \dashrightarrow 00{:}00{:}59{.}655$  many novel as say techniques for

NOTE Confidence: 0.66406729

 $00{:}00{:}59.655 \dashrightarrow 00{:}01{:}01{.}943$  identifying predictive markers to

NOTE Confidence: 0.66406729

00:01:01.943 --> 00:01:04.890 determine which tumors are sensitive

NOTE Confidence: 0.66406729

 $00{:}01{:}04.890 \dashrightarrow 00{:}01{:}07.210$  to which targeted the rapies.

NOTE Confidence: 0.66406729

 $00:01:07.210 \longrightarrow 00:01:08.730$  And this has become increasingly

NOTE Confidence: 0.66406729

00:01:08.730 --> 00:01:10.608 important as the number of targeted

NOTE Confidence: 0.66406729

 $00:01:10.608 \longrightarrow 00:01:12.128$  therapies has increased and our

- NOTE Confidence: 0.66406729
- $00:01:12.128 \dashrightarrow 00:01:14.120$  use of those drugs has increased.
- NOTE Confidence: 0.66406729
- 00:01:14.120 $\operatorname{-->}$ 00:01:16.336 And today he's going to focus on the
- NOTE Confidence: 0.66406729
- 00:01:16.336 --> 00:01:17.777 development of companion diagnostics
- NOTE Confidence: 0.66406729
- $00{:}01{:}17.777 \dashrightarrow 00{:}01{:}19.837$  for her two directed the rapies.
- NOTE Confidence: 0.66406729
- $00{:}01{:}19.840 \dashrightarrow 00{:}01{:}22.640$  I think this is particularly timely as
- NOTE Confidence: 0.66406729
- $00{:}01{:}22.640 \dashrightarrow 00{:}01{:}26.148$  the first her two targeted the rapy for non.
- NOTE Confidence: 0.66406729
- $00:01:26.150 \dashrightarrow 00:01:28.075$  Fish amplified breast cancers was
- NOTE Confidence: 0.66406729
- $00{:}01{:}28.075 \dashrightarrow 00{:}01{:}30.754$  just approved six months ago and how
- NOTE Confidence: 0.66406729
- $00:01:30.754 \dashrightarrow 00:01:32.464$  exactly we identify which patients
- NOTE Confidence: 0.66406729
- $00{:}01{:}32.464 \dashrightarrow 00{:}01{:}34.846$  are going to benefit from this therapy
- NOTE Confidence: 0.66406729
- $00:01:34.846 \dashrightarrow 00:01:37.280$  I think is a huge question and the
- NOTE Confidence: 0.66406729
- $00{:}01{:}37.280 \dashrightarrow 00{:}01{:}38.995$  one the field is struggling with and
- NOTE Confidence: 0.66406729
- 00:01:38.995 --> 00:01:40.704 David's made a lot of inroads into that
- NOTE Confidence: 0.66406729
- $00{:}01{:}40.704 \dashrightarrow 00{:}01{:}42.450$  and I think he's going to focus on,
- NOTE Confidence: 0.66406729
- $00:01:42.450 \longrightarrow 00:01:43.782$  on on that today.
- NOTE Confidence: 0.66406729

- $00:01:43.782 \longrightarrow 00:01:45.780$  So thank you for bringing this
- NOTE Confidence: 0.66406729
- $00{:}01{:}45{.}859 \dashrightarrow 00{:}01{:}47{.}560$  timely discussion to us.
- NOTE Confidence: 0.838330737692308
- 00:01:51.270 --> 00:01:53.545 OK, great. Thanks, Diane, and thanks to
- NOTE Confidence: 0.838330737692308
- $00:01:53.545 \rightarrow 00:01:55.588$  the leadership for inviting me today.
- NOTE Confidence: 0.838330737692308
- $00{:}01{:}55{.}590 \dashrightarrow 00{:}01{:}56{.}550$  But thanks especially for
- NOTE Confidence: 0.838330737692308
- 00:01:56.550 --> 00:01:57.510 Ian for introducing me.
- NOTE Confidence: 0.838330737692308
- $00{:}01{:}57{.}510 \dashrightarrow 00{:}01{:}59{.}029$  He's a world leader in this space
- NOTE Confidence: 0.838330737692308
- $00{:}01{:}59{.}029 \dashrightarrow 00{:}02{:}00{.}370$  that I'm going to talk about.
- NOTE Confidence: 0.838330737692308
- $00{:}02{:}00{.}370 \dashrightarrow 00{:}02{:}03{.}520$  That is the her two.
- NOTE Confidence: 0.838330737692308
- $00:02:03.520 \rightarrow 00:02:06.586$  80C or antibody drug conjugate space.
- NOTE Confidence: 0.838330737692308
- $00:02:06.590 \dashrightarrow 00:02:09.159$  I'll start by my title is precision
- NOTE Confidence: 0.838330737692308
- $00:02:09.159 \rightarrow 00:02:10.967$  medicine versus persuasion medicine and
- NOTE Confidence: 0.838330737692308
- $00{:}02{:}10.967 \dashrightarrow 00{:}02{:}12.887$  I'll get to what persuasion medicine
- NOTE Confidence: 0.838330737692308
- $00{:}02{:}12.887 \dashrightarrow 00{:}02{:}15.185$  is a little bit more at the end.
- NOTE Confidence: 0.838330737692308
- 00:02:15.190 00:02:16.718 And reading versus measuring.
- NOTE Confidence: 0.838330737692308
- $00:02:16.718 \rightarrow 00:02:20.070$  And measuring is what you do quantitatively.

 $00:02:20.070 \dashrightarrow 00:02:21.665$  Reading is what pathologists do

NOTE Confidence: 0.838330737692308

00:02:21.665 --> 00:02:23.754 when they look at slides and

NOTE Confidence: 0.838330737692308

 $00:02:23.754 \rightarrow 00:02:25.498$  difference between subjective and

NOTE Confidence: 0.838330737692308

 $00:02:25.498 \longrightarrow 00:02:27.242$  objective assessment of tissue.

NOTE Confidence: 0.939715525

 $00:02:29.830 \rightarrow 00:02:33.160$  Let's see. Let's start with my disclosures.

NOTE Confidence: 0.939715525

00:02:33.160 --> 00:02:36.160 As you can see, I do a fair bit of consulting

NOTE Confidence: 0.939715525

 $00:02:36.160 \dashrightarrow 00:02:38.004$  and a lot of the research in my lab,

NOTE Confidence: 0.939715525

 $00:02:38.010 \dashrightarrow 00:02:39.599$  including the work that led to this.

NOTE Confidence: 0.939715525

 $00{:}02{:}39{.}600 \dashrightarrow 00{:}02{:}41{.}595$  Most of what I'm going to present

NOTE Confidence: 0.939715525

 $00:02:41.595 \longrightarrow 00:02:43.290$  today was sponsored by companies

NOTE Confidence: 0.939715525

 $00:02:43.290 \dashrightarrow 00:02:45.250$  including Sephylon and Kanika Minolta.

NOTE Confidence: 0.91608862625

00:02:47.380 --> 00:02:50.034 So today I want to spend the next 55

NOTE Confidence: 0.91608862625

 $00:02:50.034 \rightarrow 00:02:52.092$  minutes or so talking about first and

NOTE Confidence: 0.91608862625

 $00{:}02{:}52.092 \dashrightarrow 00{:}02{:}53.580$  quick introduction to the new drugs.

NOTE Confidence: 0.91608862625

 $00{:}02{:}53.580 \dashrightarrow 00{:}02{:}54.620$  If you've heard Ian speak,

00:02:54.620 --> 00:02:55.740 I don't need to give this part,

NOTE Confidence: 0.91608862625

 $00:02:55.740 \rightarrow 00:02:58.564$  but maybe you didn't a proposed new assay

NOTE Confidence: 0.91608862625

 $00:02:58.564 \rightarrow 00:03:01.117$  for these new drugs high sensitivity

NOTE Confidence: 0.91608862625

 $00:03:01.117 \rightarrow 00:03:03.775$  would call the assay high sensitivity

NOTE Confidence: 0.91608862625

 $00{:}03{:}03{.}851 \dashrightarrow 00{:}03{:}05{.}995$  or HS or two and then CAP CLIA,

NOTE Confidence: 0.91608862625

 $00:03:06.000 \dashrightarrow 00:03:08.192$  what take, what does it take to get NOTE Confidence: 0.91608862625

 $00{:}03{:}08{.}192 \dashrightarrow 00{:}03{:}09{.}791$  something from your research lab so

NOTE Confidence: 0.91608862625

 $00:03:09.791 \longrightarrow 00:03:11.968$  that into a lab where we can deliver

NOTE Confidence: 0.91608862625

00:03:11.968 --> 00:03:13.876 information to patients and put the

NOTE Confidence: 0.91608862625

 $00:03:13.876 \longrightarrow 00:03:15.378$  results in the patient's chart.

NOTE Confidence: 0.91608862625

 $00{:}03{:}15{.}378 \dashrightarrow 00{:}03{:}17{.}650$  That's what cap CLIA is taking the new.

NOTE Confidence: 0.91608862625

 $00:03:17.650 \longrightarrow 00:03:19.514$  Say to the clinic and then finally I'll

NOTE Confidence: 0.91608862625

00:03:19.514 --> 00:03:20.933 talk about precision medicine versus

NOTE Confidence: 0.91608862625

 $00{:}03{:}20{.}933 \dashrightarrow 00{:}03{:}23{.}047$  persuasion medicine and try to talk all

NOTE Confidence: 0.91608862625

 $00{:}03{:}23{.}103 \dashrightarrow 00{:}03{:}24{.}775$  of you who are on cologists in the room

NOTE Confidence: 0.91608862625

 $00{:}03{:}24.775 \dashrightarrow 00{:}03{:}26.656$  and to not using persuasion medicine

 $00:03:26.656 \rightarrow 00:03:28.476$  and focusing on precision medicine.

NOTE Confidence: 0.8055161766666667

 $00{:}03{:}30{.}610 \dashrightarrow 00{:}03{:}32{.}869$  So this is the, the big drug that got

NOTE Confidence: 0.8055161766666667

 $00:03:32.869 \rightarrow 00:03:35.139$  the first standing ovation in 25 years

NOTE Confidence: 0.8055161766666667

 $00:03:35.139 \dashrightarrow 00:03:37.710$  as I understand at ASCO and it it's,

NOTE Confidence: 0.8055161766666667

 $00:03:37.710 \longrightarrow 00:03:39.310$  it's the same old drug,

NOTE Confidence: 0.8055161766666667

00:03:39.310 --> 00:03:41.116 it's trastuzumab underneath,

NOTE Confidence: 0.8055161766666667

 $00{:}03{:}41{.}116 \dashrightarrow 00{:}03{:}44{.}026$  but they've conjugated 8 topoisomerase

NOTE Confidence: 0.805516176666667

 $00:03:44.026 \rightarrow 00:03:47.002$  inhibitor payloads to the trastuzumab that

NOTE Confidence: 0.8055161766666667

 $00:03:47.002 \dashrightarrow 00:03:49.850$  gives you especially some special tricks.

NOTE Confidence: 0.8055161766666667

00:03:49.850 --> 00:03:51.831 First of all, it brings these highly

NOTE Confidence: 0.8055161766666667

00:03:51.831 - > 00:03:53.330 toxic payloads right to the cell.

NOTE Confidence: 0.8055161766666667

 $00{:}03{:}53{.}330 \dashrightarrow 00{:}03{:}55{.}738$  So it doesn't have the toxicity that

NOTE Confidence: 0.8055161766666667

 $00{:}03{:}55{.}738 \dashrightarrow 00{:}03{:}58{.}092$  giving the drug and the dosages that

NOTE Confidence: 0.8055161766666667

 $00{:}03{:}58.092 \dashrightarrow 00{:}04{:}00.274$  it would be given cause would cause.

NOTE Confidence: 0.8055161766666667

 $00:04:00.274 \longrightarrow 00:04:01.506$  All kinds of toxicity.

00:04:01.510 --> 00:04:03.166 But if you bring it right to the

NOTE Confidence: 0.8055161766666667

00:04:03.166 --> 00:04:04.689 salad it causes less toxicity.

NOTE Confidence: 0.8055161766666667

00:04:04.690 --> 00:04:07.448 Whereas if you, and not only that,

NOTE Confidence: 0.8055161766666667

 $00:04:07.450 \longrightarrow 00:04:09.052$  when it gets uncoupled in the

NOTE Confidence: 0.8055161766666667

 $00:04:09.052 \longrightarrow 00:04:11.406$  cell it can spill out of the cell

NOTE Confidence: 0.8055161766666667

 $00:04:11.406 \longrightarrow 00:04:12.630$  and kill neighboring cells.

NOTE Confidence: 0.8055161766666667

 $00{:}04{:}12.630 \dashrightarrow 00{:}04{:}15.558$  The so the the sort of neighborhood effect

NOTE Confidence: 0.8055161766666667

 $00{:}04{:}15.558 \dashrightarrow 00{:}04{:}19.730$  or proximity effect of the therapy.

NOTE Confidence: 0.8055161766666667

 $00{:}04{:}19.730 \dashrightarrow 00{:}04{:}21.464$  It worked really well and that's

NOTE Confidence: 0.8055161766666667

 $00:04:21.464 \longrightarrow 00:04:23.458$  why we've all heard about it that

NOTE Confidence: 0.8055161766666667

 $00{:}04{:}23.458 \dashrightarrow 00{:}04{:}25.768$  you can see very few patients were

NOTE Confidence: 0.8055161766666667

 $00{:}04{:}25.768 \dashrightarrow 00{:}04{:}27.458$  resistant but most patients had

NOTE Confidence: 0.8055161766666667

 $00{:}04{:}27{.}458 \dashrightarrow 00{:}04{:}29{.}490$  some response and there were eleven

NOTE Confidence: 0.8055161766666667

 $00:04:29.490 \longrightarrow 00:04:32.492$  CR's in the early trials and in

NOTE Confidence: 0.8055161766666667

 $00:04:32.492 \rightarrow 00:04:34.809$  fact it worked at for all patients,

NOTE Confidence: 0.8055161766666667

 $00{:}04{:}34{.}810 \dashrightarrow 00{:}04{:}36{.}390$  but especially in patients that

- NOTE Confidence: 0.8055161766666667
- $00:04:36.390 \longrightarrow 00:04:38.250$  were not amplified for her too.
- NOTE Confidence: 0.8055161766666667
- $00{:}04{:}38{.}250 \dashrightarrow 00{:}04{:}40{.}126$  So the initial trials were all in
- NOTE Confidence: 0.8055161766666667
- $00:04:40.126 \longrightarrow 00:04:42.149$  patients that had her two amplification,
- NOTE Confidence: 0.8055161766666667
- $00:04:42.150 \longrightarrow 00:04:44.004$  but then they started trials on
- NOTE Confidence: 0.8055161766666667
- $00{:}04{:}44{.}004 \dashrightarrow 00{:}04{:}45{.}979$  patients with low her two IHC 2
- NOTE Confidence: 0.8055161766666667
- $00{:}04{:}45{.}979 \dashrightarrow 00{:}04{:}47{.}970$  plus and HC1 plus and you can see
- NOTE Confidence: 0.8055161766666667
- $00:04:47.970 \longrightarrow 00:04:49.670$  the curves look pretty similar.
- NOTE Confidence: 0.805516176666667
- $00:04:49.670 \longrightarrow 00:04:51.236$  And in fact in those low,
- NOTE Confidence: 0.8055161766666667
- $00{:}04{:}51{.}240 \dashrightarrow 00{:}04{:}53{.}557$  low patients in the Destiny 4 trial,
- NOTE Confidence: 0.8055161766666667
- $00:04:53.560 \longrightarrow 00:04:54.884$  ultimately the survival curve
- NOTE Confidence: 0.8055161766666667
- 00:04:54.884 --> 00:04:56.756 looks like great, looks like this,
- NOTE Confidence: 0.8055161766666667
- $00{:}04{:}56.756 \dashrightarrow 00{:}04{:}58.508$  which is really a great improvement
- NOTE Confidence: 0.8055161766666667
- $00{:}04{:}58{.}508 \dashrightarrow 00{:}05{:}00{.}584$  in the survival curve for advanced
- NOTE Confidence: 0.8055161766666667
- $00:05:00.584 \rightarrow 00:05:02.309$  breast cancer and changing median
- NOTE Confidence: 0.8055161766666667
- $00:05:02.370 \longrightarrow 00:05:03.858$  survival from 5 to 9 months.
- NOTE Confidence: 0.8055161766666667

00:05:03.860 --> 00:05:06.512 And that's I think what ultimately

NOTE Confidence: 0.8055161766666667

 $00{:}05{:}06{.}512 \dashrightarrow 00{:}05{:}09{.}228$  has led to the popularization of this

NOTE Confidence: 0.8055161766666667

 $00:05:09.228 \dashrightarrow 00:05:11.440$  drug and the success of the drug.

NOTE Confidence: 0.8055161766666667

 $00:05:11.440 \longrightarrow 00:05:13.342$  And they said we concluded a

NOTE Confidence: 0.8055161766666667

 $00:05:13.342 \longrightarrow 00:05:15.272$  randomized 2 group open label phase

NOTE Confidence: 0.8055161766666667

 $00:05:15.272 \longrightarrow 00:05:17.054$  two trial with her too low.

NOTE Confidence: 0.8055161766666667

 $00:05:17.060 \longrightarrow 00:05:18.144$  What does that mean?

NOTE Confidence: 0.8055161766666667

 $00:05:18.144 \longrightarrow 00:05:20.244$  So that's what we'll examine the rest, but.

NOTE Confidence: 0.8055161766666667

 $00{:}05{:}20{.}244 \dashrightarrow 00{:}05{:}20{.}900$  Before we go there,

NOTE Confidence: 0.8055161766666667

 $00:05:20.900 \longrightarrow 00:05:22.036$  what about her 20?

NOTE Confidence: 0.8055161766666667

 $00:05:22.036 \rightarrow 00:05:23.740$  What about if they don't express

NOTE Confidence: 0.8055161766666667

 $00:05:23.796 \rightarrow 00:05:25.695$  any her two at all and can we tell

NOTE Confidence: 0.8055161766666667

 $00{:}05{:}25.695 \dashrightarrow 00{:}05{:}27.302$  the difference between her 20 and

NOTE Confidence: 0.8055161766666667

 $00{:}05{:}27{.}302 \dashrightarrow 00{:}05{:}29{.}580$  her two low and in fact in her two

NOTE Confidence: 0.8055161766666667

 $00{:}05{:}29.580 \dashrightarrow 00{:}05{:}31.353$  zeros and this there is a trial

NOTE Confidence: 0.8055161766666667

 $00:05:31.353 \rightarrow 00:05:33.177$  going underway that's her two less

 $00:05:33.177 \longrightarrow 00:05:35.179$  than one but greater than zero.

NOTE Confidence: 0.8055161766666667

 $00:05:35.180 \longrightarrow 00:05:36.690$  That's the Destiny 6 trial

NOTE Confidence: 0.8055161766666667

 $00:05:36.690 \rightarrow 00:05:37.596$  hasn't reported yet.

NOTE Confidence: 0.8055161766666667

 $00:05:37.600 \rightarrow 00:05:39.832$  But there's also the her 20 equal 0

NOTE Confidence: 0.8055161766666667

00:05:39.832 --> 00:05:41.912 Daisy trial which was a small trial

NOTE Confidence: 0.8055161766666667

 $00{:}05{:}41{.}912 \dashrightarrow 00{:}05{:}43{.}843$  in France where there was clearly

NOTE Confidence: 0.8055161766666667

 $00:05:43.843 \rightarrow 00:05:45.893$  in these waterfall plots clearly

NOTE Confidence: 0.8055161766666667

 $00:05:45.893 \rightarrow 00:05:47.884$  patients that benefited from drug

NOTE Confidence: 0.8055161766666667

 $00:05:47.884 \rightarrow 00:05:50.980$  even though they had a hurt 2 = 0.

NOTE Confidence: 0.8055161766666667

 $00:05:50.980 \longrightarrow 00:05:53.052$  So is this the why is it important

NOTE Confidence: 0.8055161766666667

 $00{:}05{:}53{.}052 \dashrightarrow 00{:}05{:}54{.}816$  to understand this and have good

NOTE Confidence: 0.805516176666667

 $00{:}05{:}54{.}816 \dashrightarrow 00{:}05{:}56{.}301$  diagnostics for it because this

NOTE Confidence: 0.8055161766666667

00:05:56.301 --> 00:05:58.059 drug is the tip of the iceberg.

NOTE Confidence: 0.8055161766666667

 $00{:}05{:}58{.}060 \dashrightarrow 00{:}05{:}59{.}476$  Here's a list of other drugs

NOTE Confidence: 0.8055161766666667

 $00{:}05{:}59{.}476 \dashrightarrow 00{:}06{:}01{.}100$  which there's no way you can read,

 $00:06:01.100 \longrightarrow 00:06:02.396$  but all of these drugs are,

NOTE Confidence: 0.8055161766666667

 $00{:}06{:}02{.}400 \dashrightarrow 00{:}06{:}04{.}380$  are all these are targets for

NOTE Confidence: 0.8055161766666667

 $00{:}06{:}04.380 \dashrightarrow 00{:}06{:}05.784$  ADC's in clinical trials.

NOTE Confidence: 0.8055161766666667

00:06:05.784 --> 00:06:08.016 So I think ADC's may become very

NOTE Confidence: 0.8055161766666667

 $00{:}06{:}08{.}016 \dashrightarrow 00{:}06{:}09{.}780$  important for oncology in the next

NOTE Confidence: 0.861392332

 $00:06:09.835 \dashrightarrow 00:06:11.565$  few years and equally important

NOTE Confidence: 0.861392332

00:06:11.565 --> 00:06:13.295 will be companion diagnostics that

NOTE Confidence: 0.861392332

 $00{:}06{:}13.355 \dashrightarrow 00{:}06{:}15.149$  actually pick the right patients as

NOTE Confidence: 0.861392332

 $00:06:15.149 \dashrightarrow 00:06:16.840$  opposed to giving the drug because NOTE Confidence: 0.861392332

 $00:06:16.840 \dashrightarrow 00:06:18.800$  unlike when we know the tiger it so NOTE Confidence: 0.861392332

 $00{:}06{:}18.852 \dashrightarrow 00{:}06{:}20.684$  well and we know how the drug works.

NOTE Confidence: 0.861392332

 $00:06:20.690 \rightarrow 00:06:22.237$  It's really important to be able to

NOTE Confidence: 0.861392332

 $00:06:22.237 \longrightarrow 00:06:23.893$  pick the right target or to pick

NOTE Confidence: 0.861392332

 $00:06:23.893 \rightarrow 00:06:25.068$  the right patients that express

NOTE Confidence: 0.861392332

 $00:06:25.068 \longrightarrow 00:06:26.369$  the right amount of target.

NOTE Confidence: 0.861392332

 $00:06:26.370 \longrightarrow 00:06:27.390$  So what do we do now?

- NOTE Confidence: 0.861392332
- $00:06:27.390 \rightarrow 00:06:29.378$  So this is the standard practice guidelines,
- NOTE Confidence: 0.861392332
- 00:06:29.380 --> 00:06:32.488 ASCO CAP guidelines in 2018 and
- NOTE Confidence: 0.861392332
- $00:06:32.490 \rightarrow 00:06:35.106$  these guidelines are how we practice
- NOTE Confidence: 0.861392332
- $00:06:35.106 \rightarrow 00:06:36.850$  as pathologists in assessment
- NOTE Confidence: 0.861392332
- $00:06:36.924 \longrightarrow 00:06:38.380$  of her two expression.
- NOTE Confidence: 0.861392332
- $00:06:38.380 \longrightarrow 00:06:41.220$  And this is the algorithm for what
- NOTE Confidence: 0.861392332
- $00{:}06{:}41.220 \dashrightarrow 00{:}06{:}43.085$  we look at when we look at the slide
- NOTE Confidence: 0.861392332
- 00:06:43.085 --> 00:06:44.935 circumferential staining that is complete,
- NOTE Confidence: 0.861392332
- $00:06:44.940 \longrightarrow 00:06:47.517$  intense and greater than 10% of the cells.
- NOTE Confidence: 0.861392332
- $00{:}06{:}47{.}517 \dashrightarrow 00{:}06{:}48{.}712$  That makes the three plus
- NOTE Confidence: 0.861392332
- $00:06:48.712 \longrightarrow 00:06:50.139$  and then we have a 2 + 1 + .
- NOTE Confidence: 0.861392332
- $00:06:50.140 \longrightarrow 00:06:51.496$  I won't go through them all,
- NOTE Confidence: 0.861392332
- 00:06:51.500 -> 00:06:53.220 but they're kind of summarized
- NOTE Confidence: 0.861392332
- $00{:}06{:}53.220 \dashrightarrow 00{:}06{:}54.940$  here where one no staining,
- NOTE Confidence: 0.861392332
- 00:06:54.940 --> 00:06:57.212 no membrane staining observed is a 0 +
- NOTE Confidence: 0.861392332

 $00:06:57.212 \longrightarrow 00:06:59.551$  1 is faint partial membrane staining

NOTE Confidence: 0.861392332

 $00:06:59.551 \rightarrow 00:07:02.360$  and weak to moderate staining is +2.

NOTE Confidence: 0.861392332

 $00:07:02.360 \longrightarrow 00:07:04.898$  That's kind of subjective. In fact.

NOTE Confidence: 0.861392332

 $00{:}07{:}04.900 \dashrightarrow 00{:}07{:}06.538$  How well can we do that and

NOTE Confidence: 0.861392332

 $00:07:06.538 \longrightarrow 00:07:07.460$  how important is it?

NOTE Confidence: 0.861392332

 $00{:}07{:}07{.}460 \dashrightarrow 00{:}07{.}07{.}754$  Well.

NOTE Confidence: 0.861392332

 $00{:}07{:}07{.}754 \dashrightarrow 00{:}07{:}09{.}812$  It used to be important to tell

NOTE Confidence: 0.861392332

 $00:07:09.812 \longrightarrow 00:07:11.743$  the heart threes the three

NOTE Confidence: 0.861392332

00:07:11.743 --> 00:07:13.657 pluses from the others and the

NOTE Confidence: 0.861392332

 $00:07:13.725 \dashrightarrow 00:07:15.729$  two pluses were they the reflex.

NOTE Confidence: 0.861392332

 $00:07:15.730 \dashrightarrow 00:07:17.578$  But now it's important to have this CAD.

NOTE Confidence: 0.861392332

 $00:07:17.580 \longrightarrow 00:07:19.589$  The new category is far too low.

NOTE Confidence: 0.861392332

 $00:07:19.590 \longrightarrow 00:07:20.530$  And how many are there?

NOTE Confidence: 0.861392332

 $00:07:20.530 \longrightarrow 00:07:21.634$  There's a lot,

NOTE Confidence: 0.861392332

 $00{:}07{:}21.634 \dashrightarrow 00{:}07{:}24.525$  maybe as many as 65 or 70% of the

NOTE Confidence: 0.861392332

 $00:07:24.525 \rightarrow 00:07:26.890$  patients are thought to fall into this low,

00:07:26.890 --> 00:07:28.390 her two low category which means

NOTE Confidence: 0.861392332

 $00{:}07{:}28.390 \dashrightarrow 00{:}07{:}30.190$  a lot of patients could get drug,

NOTE Confidence: 0.861392332

 $00{:}07{:}30{.}190 \dashrightarrow 00{:}07{:}31{.}999$  but it also means that we need to be

NOTE Confidence: 0.861392332

 $00{:}07{:}31{.}999 \dashrightarrow 00{:}07{:}34{.}051$  as accurate as we can and assigning

NOTE Confidence: 0.861392332

00:07:34.051 --> 00:07:35.760 those patients because we don't want

NOTE Confidence: 0.861392332

 $00:07:35.760 \longrightarrow 00:07:37.576$  the her two zeros to get the drug

NOTE Confidence: 0.861392332

 $00:07:37.580 \longrightarrow 00:07:38.756$  if they aren't going to benefit.

NOTE Confidence: 0.861392332

 $00:07:38.760 \longrightarrow 00:07:39.856$  Well, maybe we do.

NOTE Confidence: 0.861392332

 $00:07:39.856 \longrightarrow 00:07:41.226$  We'll talk about that later.

NOTE Confidence: 0.861392332

00:07:41.230 --> 00:07:43.295 But so how do we know how,

NOTE Confidence: 0.861392332

 $00:07:43.300 \longrightarrow 00:07:44.406$  how well do we do at this?

NOTE Confidence: 0.861392332

00:07:44.410 --> 00:07:45.052 Her too.

NOTE Confidence: 0.861392332

 $00{:}07{:}45.052 \dashrightarrow 00{:}07{:}47.299$  So I'm fortunate to be on the

NOTE Confidence: 0.861392332

00:07:47.299 --> 00:07:48.461 immunohistochemistry committee of

NOTE Confidence: 0.861392332

 $00{:}07{:}48.461 \dashrightarrow 00{:}07{:}50.406$  the College of American Pathologists.

 $00:07:50.410 \longrightarrow 00:07:52.258$  And so I get access to the

NOTE Confidence: 0.861392332

00:07:52.258 --> 00:07:53.720 surveys that make Clea labs,

NOTE Confidence: 0.861392332

 $00{:}07{:}53.720 \dashrightarrow 00{:}07{:}54.620$  what CLIA labs are.

NOTE Confidence: 0.861392332

 $00:07:54.620 \longrightarrow 00:07:55.070$  That is,

NOTE Confidence: 0.861392332

 $00{:}07{:}55{.}070 \dashrightarrow 00{:}07{:}56{.}862$  for a CLIA lab or clinical lab

NOTE Confidence: 0.861392332

 $00{:}07{:}56.862 \dashrightarrow 00{:}07{:}58.428$  to return data to the chart,

NOTE Confidence: 0.861392332

 $00:07:58.430 \longrightarrow 00:08:00.038$  they have to do a survey twice a

NOTE Confidence: 0.861392332

 $00:08:00.038 \rightarrow 00:08:01.724$  year to show that they're competent

NOTE Confidence: 0.861392332

 $00{:}08{:}01{.}724 \dashrightarrow 00{:}08{:}03{.}566$  and effective at doing the assay.

NOTE Confidence: 0.861392332

 $00{:}08{:}03{.}570 \dashrightarrow 00{:}08{:}05{.}838$  And here's the surveys for an atomic

NOTE Confidence: 0.861392332

 $00{:}08{:}05{.}838$  -->  $00{:}08{:}08{.}709$  pathology for her two using a tissue NOTE Confidence: 0.861392332

 $00:08:08.709 \rightarrow 00:08:11.030$  microarray. This is her to a 2020.

NOTE Confidence: 0.861392332

 $00:08:11.030 \longrightarrow 00:08:12.974$  So it was the fall survey or the

NOTE Confidence: 0.861392332

 $00:08:12.974 \longrightarrow 00:08:14.874$  spring survey from 2020 from the

NOTE Confidence: 0.861392332

00:08:14.874 --> 00:08:16.574 College of American Pilot Pathologists.

NOTE Confidence: 0.861392332

 $00:08:16.580 \rightarrow 00:08:18.148$  And you can see my colleagues here,

- NOTE Confidence: 0.861392332
- $00:08:18.150 \rightarrow 00:08:20.005$  including myself, who are on this committee.
- NOTE Confidence: 0.861392332
- $00{:}08{:}20{.}010 \dashrightarrow 00{:}08{:}21{.}697$  And when we looked at these surveys,
- NOTE Confidence: 0.861392332
- $00:08:21.700 \rightarrow 00:08:23.765$  we noticed that four, six and seven,
- NOTE Confidence: 0.861392332
- $00:08:23.770 \dashrightarrow 00:08:26.770$  that is 3 out of 10 did not reach consensus.
- NOTE Confidence: 0.861392332
- $00:08:26.770 \longrightarrow 00:08:29.382$  That means that of the 1400 labs
- NOTE Confidence: 0.861392332
- $00:08:29.382 \rightarrow 00:08:31.750$  in the in the world that did this,
- NOTE Confidence: 0.861392332
- $00:08:31.750 \longrightarrow 00:08:33.898$  they couldn't come to an agreement.
- NOTE Confidence: 0.861392332
- $00:08:33.900 \longrightarrow 00:08:34.362$  That is,
- NOTE Confidence: 0.861392332
- $00{:}08{:}34{.}362 \dashrightarrow 00{:}08{:}35{.}517$  you need to have 90%
- NOTE Confidence: 0.898946901666667
- $00:08:35.520 \longrightarrow 00:08:37.164$  consensus to have agreement.
- NOTE Confidence: 0.8989469016666667
- $00:08:37.164 \longrightarrow 00:08:38.758$  In fact, if we look at this one,
- NOTE Confidence: 0.8989469016666667
- $00{:}08{:}38{.}760 \dashrightarrow 00{:}08{:}39{.}364$  it's interesting.
- NOTE Confidence: 0.8989469016666667
- $00{:}08{:}39{.}364 \dashrightarrow 00{:}08{:}41{.}780$  This is one of the cases that didn't
- NOTE Confidence: 0.898946901666667
- $00{:}08{:}41.841 \dashrightarrow 00{:}08{:}43.521$  come to agreement and that was
- NOTE Confidence: 0.898946901666667
- $00:08:43.521 \rightarrow 00:08:45.259$  because there was a big discordance
- NOTE Confidence: 0.898946901666667

 $00:08:45.259 \longrightarrow 00:08:47.219$  in the number of called 0 versus

NOTE Confidence: 0.898946901666667

 $00{:}08{:}47{.}219 \dashrightarrow 00{:}08{:}48{.}826$  1 and there were a fair number

NOTE Confidence: 0.898946901666667

 $00:08:48.826 \longrightarrow 00:08:50.360$  that even called it two or three.

NOTE Confidence: 0.898946901666667

 $00:08:50.360 \longrightarrow 00:08:51.335$  So that's troublesome.

NOTE Confidence: 0.898946901666667

 $00{:}08{:}51{.}335 \dashrightarrow 00{:}08{:}54{.}003$  If we're testing these labs twice a year

NOTE Confidence: 0.898946901666667

 $00{:}08{:}54{.}003 \dashrightarrow 00{:}08{:}56{.}019$  and we're assuring that they're giving

NOTE Confidence: 0.8989469016666667

 $00:08:56.019 \rightarrow 00:08:58.038$  the right answer for the patients,

NOTE Confidence: 0.898946901666667

 $00:08:58.040 \rightarrow 00:09:00.147$  how can you have that much difference

NOTE Confidence: 0.8989469016666667

 $00:09:00.147 \dashrightarrow 00:09:02.559$  between zero and one that it's almost 5050.

NOTE Confidence: 0.898946901666667

 $00:09:02.560 \rightarrow 00:09:05.440$  So since I I'm on the CAP committee,

NOTE Confidence: 0.8989469016666667

 $00{:}09{:}05{.}440 \dashrightarrow 00{:}09{:}06{.}945$  I could ask for the data from

NOTE Confidence: 0.898946901666667

 $00:09:06.945 \longrightarrow 00:09:07.950$  the last few years.

NOTE Confidence: 0.898946901666667

 $00{:}09{:}07{.}950 \dashrightarrow 00{:}09{.}09{.}485$  And here's the data from

NOTE Confidence: 0.8989469016666667

 $00:09:09.485 \longrightarrow 00:09:11.655$  the lab from 2019 and 2020.

NOTE Confidence: 0.898946901666667

 $00{:}09{:}11.655 \dashrightarrow 00{:}09{:}13.730$  And of the 80 cases,

NOTE Confidence: 0.898946901666667

 $00{:}09{:}13.730 \dashrightarrow 00{:}09{:}15.698$  fifteen of those cases showed a

- NOTE Confidence: 0.898946901666667
- $00:09:15.698 \longrightarrow 00:09:17.329$  discordance of greater than 25%.
- NOTE Confidence: 0.8989469016666667
- $00{:}09{:}17{.}329 \dashrightarrow 00{:}09{:}19{.}243$  And that's shown in these pie
- NOTE Confidence: 0.8989469016666667
- $00{:}09{:}19{.}243 \dashrightarrow 00{:}09{:}21{.}063$  charts here where the zeros are
- NOTE Confidence: 0.898946901666667
- $00{:}09{:}21.063 \dashrightarrow 00{:}09{:}22.911$  blue and the ones are red and
- NOTE Confidence: 0.8989469016666667
- $00:09:22.978 \dashrightarrow 00:09:25.066$  anything higher than one is black.
- NOTE Confidence: 0.898946901666667
- $00:09:25.070 \rightarrow 00:09:25.640$  Two and three,
- NOTE Confidence: 0.8989469016666667
- $00:09:25.640 \rightarrow 00:09:27.210$  since we're not going to focus on that.
- NOTE Confidence: 0.898946901666667
- $00:09:27.210 \longrightarrow 00:09:28.154$  So we we did,
- NOTE Confidence: 0.898946901666667
- $00:09:28.154 \dashrightarrow 00:09:30.056$  we thought is this really, you know,
- NOTE Confidence: 0.8989469016666667
- $00:09:30.056 \rightarrow 00:09:31.130$  this is concerning,
- NOTE Confidence: 0.8989469016666667
- $00:09:31.130 \longrightarrow 00:09:33.106$  but you know what this is tissue microarrays.
- NOTE Confidence: 0.8989469016666667
- $00:09:33.110 \dashrightarrow 00:09:34.982$  This is not what happens in the real world.
- NOTE Confidence: 0.8989469016666667
- $00:09:34.990 \longrightarrow 00:09:37.078$  So then we did a study of real
- NOTE Confidence: 0.8989469016666667
- $00{:}09{:}37.078 \dashrightarrow 00{:}09{:}38.240$  world core biopsies.
- NOTE Confidence: 0.898946901666667
- $00{:}09{:}38{.}240 \dashrightarrow 00{:}09{:}40{.}352$  And enrolled 18 pathologists from 15
- NOTE Confidence: 0.898946901666667

 $00{:}09{:}40.352 \dashrightarrow 00{:}09{:}42.092$  institutions around the United States

NOTE Confidence: 0.898946901666667

 $00{:}09{:}42.092 \dashrightarrow 00{:}09{:}44.038$  and ask them to read actual core

NOTE Confidence: 0.898946901666667

 $00:09:44.038 \rightarrow 00:09:45.856$  biopsies that have been read at Yale.

NOTE Confidence: 0.898946901666667

 $00:09:45.860 \longrightarrow 00:09:48.032$  We collected 170 cases from Yale

NOTE Confidence: 0.898946901666667

00:09:48.032 --> 00:09:50.914 and had them score them according to

NOTE Confidence: 0.8989469016666667

00:09:50.914 --> 00:09:53.638 the ASCO CAP guidelines before the

NOTE Confidence: 0.8989469016666667

 $00{:}09{:}53.638 \dashrightarrow 00{:}09{:}55.275$  publication and the popularization

NOTE Confidence: 0.8989469016666667

 $00:09:55.275 \rightarrow 00:09:57.858$  of her two one plus versus 0.

NOTE Confidence: 0.8989469016666667

 $00:09:57.860 \rightarrow 00:09:59.652$  So they didn't know they were just

NOTE Confidence: 0.8989469016666667

 $00:09:59.652 \rightarrow 00:10:01.384$  doing the ASCO CAP guidelines as

NOTE Confidence: 0.898946901666667

 $00:10:01.384 \rightarrow 00:10:03.593$  they always have, and scoring 0123.

NOTE Confidence: 0.8989469016666667

00:10:03.593 --> 00:10:05.317 And what they did,

NOTE Confidence: 0.8989469016666667

 $00:10:05.320 \rightarrow 00:10:07.056$  what they're scoring looked like was this.

NOTE Confidence: 0.898946901666667

 $00:10:07.060 \rightarrow 00:10:08.467$  That is, the Blues were the zeros.

NOTE Confidence: 0.8989469016666667

 $00:10:08.470 \rightarrow 00:10:10.468$  This is the percent of pathologists.

NOTE Confidence: 0.8989469016666667

 $00:10:10.470 \longrightarrow 00:10:11.894$  That scored at 0,

- NOTE Confidence: 0.898946901666667
- $00:10:11.894 \longrightarrow 00:10:14.030$  so a fair number agreed that
- NOTE Confidence: 0.8989469016666667
- $00:10:14.030 \longrightarrow 00:10:15.438$  that there were zeros.
- NOTE Confidence: 0.8989469016666667
- 00:10:15.438 --> 00:10:18.370 There were 92 cases that were discordant,
- NOTE Confidence: 0.8989469016666667
- $00:10:18.370 \longrightarrow 00:10:19.822$  and of those,
- NOTE Confidence: 0.8989469016666667
- $00{:}10{:}19{.}822 \dashrightarrow 00{:}10{:}23{.}210$ 9269 were discordant between zero and one,
- NOTE Confidence: 0.8989469016666667
- $00{:}10{:}23.210 \dashrightarrow 00{:}10{:}24.875$  and only twenty were discordant
- NOTE Confidence: 0.8989469016666667
- $00:10:24.875 \longrightarrow 00:10:26.207$  between 2:00 and 3:00.
- NOTE Confidence: 0.898946901666667
- $00:10:26.210 \longrightarrow 00:10:28.438$  So this actually was.
- NOTE Confidence: 0.898946901666667
- 00:10:28.438 --> 00:10:30.109 Through many reviewers,
- NOTE Confidence: 0.898946901666667
- 00:10:30.110 --> 00:10:34.457 ultimately got us published in JAMA Oncology.
- NOTE Confidence: 0.8989469016666667
- 00:10:34.460 --> 00:10:35.978 How come it's not advancing now?
- NOTE Confidence: 0.85056264125
- $00:10:38.430 \longrightarrow 00:10:43.566$  Oh, hold on. I lost my laser pointer.
- NOTE Confidence: 0.85056264125
- $00{:}10{:}43.570 \dashrightarrow 00{:}10{:}45.386$  Microsoft doesn't want me to do this now.
- NOTE Confidence: 0.85056264125
- 00:10:45.390 --> 00:10:46.960 It's the screen has turned
- NOTE Confidence: 0.85056264125
- $00:10:46.960 \rightarrow 00:10:48.530$  Gray as it's saying restart.
- NOTE Confidence: 0.85056264125

 $00:10:48.530 \longrightarrow 00:10:49.643$  I probably shouldn't.

NOTE Confidence: 0.85056264125

 $00:10:49.643 \longrightarrow 00:10:51.498$  I should probably wait for

NOTE Confidence: 0.85056264125

 $00:10:51.498 \longrightarrow 00:10:52.989$  the program to respond.

NOTE Confidence: 0.85056264125

 $00:10:52.990 \longrightarrow 00:10:54.194$  Very sorry about this,

NOTE Confidence: 0.85056264125

 $00{:}10{:}54{.}194 \dashrightarrow 00{:}10{:}56{.}627$  but suffice it to say that I'll skip

NOTE Confidence: 0.85056264125

 $00{:}10{:}56.627 \dashrightarrow 00{:}10{:}58.883$  the next slide so we can keep going.

NOTE Confidence: 0.85056264125

 $00:10:58.890 \longrightarrow 00:11:00.400$  The next slide was after

NOTE Confidence: 0.85056264125

 $00:11:00.400 \rightarrow 00:11:01.910$  many review rounds of review,

NOTE Confidence: 0.85056264125

 $00:11:01.910 \rightarrow 00:11:03.750$  we did get this published in JAMA Oncology,

NOTE Confidence: 0.85056264125

 $00:11:03.750 \longrightarrow 00:11:04.890$  but weren't allowed to say

NOTE Confidence: 0.85056264125

 $00:11:04.890 \longrightarrow 00:11:06.030$  what we wanted to say,

NOTE Confidence: 0.85056264125

00:11:06.030 --> 00:11:07.896 which is that there's really a

NOTE Confidence: 0.85056264125

 $00{:}11{:}07{.}896 \dashrightarrow 00{:}11{:}09{.}462$  great discordance between zero and

NOTE Confidence: 0.85056264125

 $00{:}11{:}09{.}462 \dashrightarrow 00{:}11{:}11{.}052$  one and not so much discordance

NOTE Confidence: 0.85056264125

 $00{:}11{:}11{.}052 \dashrightarrow 00{:}11{:}12{.}160$  between 2:00 and 3:00.

NOTE Confidence: 0.85056264125

00:11:12.160 --> 00:11:13.399 And I don't know if we have

- NOTE Confidence: 0.85056264125
- 00:11:13.399 --> 00:11:14.460 should I restart the program?
- NOTE Confidence: 0.85056264125
- 00:11:14.460 --> 00:11:15.980 I don't know if we have any IT
- NOTE Confidence: 0.85056264125
- $00:11:15.980 \rightarrow 00:11:17.448$  people here that or how long we're,
- NOTE Confidence: 0.85056264125
- 00:11:17.450 --> 00:11:17.886 you know,
- NOTE Confidence: 0.85056264125
- $00:11:17.886 \longrightarrow 00:11:19.630$  we'll be here for the next 45 minutes
- NOTE Confidence: 0.85056264125
- $00{:}11{:}19.679$  -->  $00{:}11{:}21.485$  waiting for the computer to come along.
- NOTE Confidence: 0.865999128571429
- $00:11:25.290 \rightarrow 00:11:28.076$  Wait to respond or restart the program.
- NOTE Confidence: 0.865999128571429
- $00:11:28.080 \rightarrow 00:11:29.494$  Maybe I should restart the program and
- NOTE Confidence: 0.865999128571429
- $00{:}11{:}29{.}494 \dashrightarrow 00{:}11{:}30{.}910$  that will take several minutes too.
- NOTE Confidence: 0.74473373
- 00:11:31.260 --> 00:11:32.646 It's just it's just not rebooting
- NOTE Confidence: 0.74473373
- $00:11:32.646 \rightarrow 00:11:36.560$  the computer, it's just. Yeah.
- NOTE Confidence: 0.9146245066666667
- 00:11:36.560 --> 00:11:40.718 Let's try again. Yeah, we're good.
- NOTE Confidence: 0.9146245066666667
- 00:11:40.718 --> 00:11:43.094 We're good. Sorry about that. OK.
- NOTE Confidence: 0.9146245066666667
- $00{:}11{:}43.094 \dashrightarrow 00{:}11{:}45.350$  We saw all those things already.
- NOTE Confidence: 0.9146245066666667
- $00{:}11{:}45{.}350 \dashrightarrow 00{:}11{:}49{.}480$  Let's go to. The study that was in
- NOTE Confidence: 0.9146245066666667

 $00{:}11{:}49{.}480 \dashrightarrow 00{:}11{:}51{.}768$  JAMA Oncology was here and this is

NOTE Confidence: 0.9146245066666667

 $00{:}11{:}51{.}768 \dashrightarrow 00{:}11{:}54{.}261$  what was the this is the figure and

NOTE Confidence: 0.9146245066666667

00:11:54.261 --> 00:11:56.367 and Eileen Fernandez was the lead NOTE Confidence: 0.9146245066666667

 $00:11:56.367 \rightarrow 00:11:58.726$  on this study in my lab and she.

NOTE Confidence: 0.9146245066666667

00:11:58.730 --> 00:12:00.480 Did the analysis that is shown here

NOTE Confidence: 0.9146245066666667

 $00:12:00.480 \rightarrow 00:12:02.385$  that shows that there's a lot more

NOTE Confidence: 0.9146245066666667

00:12:02.385 --> 00:12:03.760 discordance between zero and one

NOTE Confidence: 0.9146245066666667

 $00:12:03.760 \longrightarrow 00:12:05.605$  than there is between 2:00 and 3:00.

NOTE Confidence: 0.9146245066666667

 $00{:}12{:}05{.}610 \dashrightarrow 00{:}12{:}07{.}605$  And for two we have a solution.

NOTE Confidence: 0.9146245066666667

 $00:12:07.610 \longrightarrow 00:12:09.050$  For two we can do fish,

NOTE Confidence: 0.9146245066666667

 $00{:}12{:}09{.}050 \dashrightarrow 00{:}12{:}10{.}970$  so we have a orthogonal assay.

NOTE Confidence: 0.9146245066666667

 $00:12:10.970 \longrightarrow 00:12:12.474$  What do we do between zero and one?

NOTE Confidence: 0.9146245066666667

 $00:12:12.480 \longrightarrow 00:12:14.160$  Well, we don't have a solution yet.

NOTE Confidence: 0.9146245066666667

 $00{:}12{:}14.160 \dashrightarrow 00{:}12{:}15.904$  That's what I'll show you in a minute.

NOTE Confidence: 0.9146245066666667

 $00:12:15.910 \longrightarrow 00:12:18.694$  But also you can look at this analysis

NOTE Confidence: 0.9146245066666667

 $00:12:18.694 \rightarrow 00:12:21.286$  which which shows you this is a work

 $00:12:21.286 \rightarrow 00:12:24.221$  done by Jack Robbins in the lab with

NOTE Confidence: 0.9146245066666667

00:12:24.221 --> 00:12:26.120 Eileen Fernandez showing the percentage

NOTE Confidence: 0.9146245066666667

 $00:12:26.120 \longrightarrow 00:12:29.080$  of people that called 0 versus called one.

NOTE Confidence: 0.9146245066666667

 $00:12:29.080 \longrightarrow 00:12:30.886$  And so if your pathologist #18 and

NOTE Confidence: 0.9146245066666667

 $00{:}12{:}30.886 \dashrightarrow 00{:}12{:}32.772$  these are all currently signing out

NOTE Confidence: 0.9146245066666667

 $00{:}12{:}32{.}772 \dashrightarrow 00{:}12{:}34{.}872$  pathologists most with more than five

NOTE Confidence: 0.9146245066666667

 $00:12:34.872 \rightarrow 00:12:37.056$  years of experience around the country.

NOTE Confidence: 0.9146245066666667

 $00:12:37.060 \longrightarrow 00:12:39.274$  So these are not residents or not to say

NOTE Confidence: 0.9146245066666667

 $00{:}12{:}39{.}274 \dashrightarrow 00{:}12{:}41{.}599$  that residents can't do this just as well.

NOTE Confidence: 0.9146245066666667

 $00:12:41.600 \dashrightarrow 00:12:43.365$  But these are not residents

NOTE Confidence: 0.9146245066666667

 $00:12:43.365 \longrightarrow 00:12:44.777$  or or or laboratorians.

NOTE Confidence: 0.9146245066666667

 $00:12:44.780 \longrightarrow 00:12:46.640$  These are sign up with ologists.

NOTE Confidence: 0.9146245066666667

00:12:46.640 --> 00:12:48.999 And if you're pathologist 18 you only

NOTE Confidence: 0.9146245066666667

 $00:12:48.999 \longrightarrow 00:12:51.657$  score 15% of the patients with a 0,

NOTE Confidence: 0.9146245066666667

 $00:12:51.660 \rightarrow 00:12:53.040$  but if your pathologist number one,

- $00:12:53.040 \longrightarrow 00:12:54.090$  you have 44%.
- NOTE Confidence: 0.9146245066666667
- $00:12:54.090 \rightarrow 00:12:56.540$  So whether or not you get trustors,
- NOTE Confidence: 0.9146245066666667
- 00:12:56.540 --> 00:12:57.130 mab drugs,
- NOTE Confidence: 0.9146245066666667
- $00:12:57.130 \rightarrow 00:12:59.195$  tecan depends on who your pathologist is.
- NOTE Confidence: 0.9146245066666667
- $00:12:59.200 \rightarrow 00:13:01.846$  That doesn't sound like a great idea to me.
- NOTE Confidence: 0.9146245066666667
- $00{:}13{:}01{.}850 \dashrightarrow 00{:}13{:}03{.}810$  So what we asked is how many people
- NOTE Confidence: 0.9146245066666667
- $00:13:03.810 \longrightarrow 00:13:05.760$  do you need to make sure that
- NOTE Confidence: 0.9146245066666667
- $00:13:05.760 \longrightarrow 00:13:07.570$  an assay agrees with each other?
- NOTE Confidence: 0.9146245066666667
- $00:13:07.570 \rightarrow 00:13:09.826$  And we, we invented this with gang hand.
- NOTE Confidence: 0.9146245066666667
- $00{:}13{:}09{.}830 \dashrightarrow 00{:}13{:}12{.}630$  We invented this system to realize that
- NOTE Confidence: 0.9146245066666667
- $00{:}13{:}12.630 \dashrightarrow 00{:}13{:}14.415$  there's 21,000 pathologists just in the
- NOTE Confidence: 0.9146245066666667
- $00:13:14.415 \rightarrow 00:13:17.027$  US and at that and 100,000 in the world.
- NOTE Confidence: 0.9146245066666667
- 00:13:17.030 --> 00:13:18.806 So how many do we need to decide
- NOTE Confidence: 0.9146245066666667
- $00:13:18.806 \rightarrow 00:13:20.389$  whether or not an essay is good?
- NOTE Confidence: 0.9146245066666667
- $00:13:20.390 \rightarrow 00:13:22.581$  And so we there, there is actually
- NOTE Confidence: 0.9146245066666667
- $00:13:22.581 \rightarrow 00:13:24.089$  no statistical method for this.

- NOTE Confidence: 0.9146245066666667
- $00{:}13{:}24.090 \dashrightarrow 00{:}13{:}26.334$  So we simply decided to plot
- NOTE Confidence: 0.9146245066666667
- $00{:}13{:}26{.}334 \dashrightarrow 00{:}13{:}27{.}830$  the overall percent agreement.
- NOTE Confidence: 0.9146245066666667
- $00{:}13{:}27.830 \dashrightarrow 00{:}13{:}30.116$  That's what overall LPA stands for
- NOTE Confidence: 0.9146245066666667
- $00{:}13{:}30{.}116 \dashrightarrow 00{:}13{:}32{.}240$  versus the observers or readers.
- NOTE Confidence: 0.9146245066666667
- $00:13:32.240 \longrightarrow 00:13:34.728$  And what you see is that the more
- NOTE Confidence: 0.9146245066666667
- $00:13:34.728 \longrightarrow 00:13:35.750$  observers you have,
- NOTE Confidence: 0.9146245066666667
- $00:13:35.750 \longrightarrow 00:13:36.870$  the less agreement you have,
- NOTE Confidence: 0.9146245066666667
- $00:13:36.870 \longrightarrow 00:13:37.533$  which makes sense.
- NOTE Confidence: 0.9146245066666667
- 00:13:37.533 --> 00:13:38.638 The more people you ask,
- NOTE Confidence: 0.9146245066666667
- $00:13:38.640 \longrightarrow 00:13:39.592$  the more discordance you're
- NOTE Confidence: 0.9146245066666667
- 00:13:39.592 --> 00:13:41.020 going to get in your answers,
- NOTE Confidence: 0.9146245066666667
- $00:13:41.020 \longrightarrow 00:13:42.154$  just mathematical truism.
- NOTE Confidence: 0.9146245066666667
- $00{:}13{:}42{.}154 \dashrightarrow 00{:}13{:}44{.}800$  And so does this actually work and
- NOTE Confidence: 0.9146245066666667
- $00:13:44.873 \longrightarrow 00:13:47.015$  can this be used to assess as says?
- NOTE Confidence: 0.9146245066666667
- $00:13:47.020 \longrightarrow 00:13:48.256$  So here's estrogen receptor.
- NOTE Confidence: 0.9146245066666667

00:13:48.256 --> 00:13:49.801 Turns out we're really good

NOTE Confidence: 0.9146245066666667

 $00{:}13{:}49{.}801 \dashrightarrow 00{:}13{:}51{.}110$  at estrogen receptor.

NOTE Confidence: 0.9146245066666667

 $00:13:51.110 \longrightarrow 00:13:53.876$  If you have a quartet of

NOTE Confidence: 0.9146245066666667

00:13:53.876 --> 00:13:55.720 pathologists read estrogen receptor,

NOTE Confidence: 0.9146245066666667

 $00:13:55.720 \longrightarrow 00:13:58.100$  all four of them will agree somewhere

NOTE Confidence: 0.9146245066666667

 $00{:}13{:}58{.}100 \dashrightarrow 00{:}14{:}01{.}000$  between 85 and 95% of the time.

NOTE Confidence: 0.9146245066666667

 $00:14:01.000 \longrightarrow 00:14:01.798$  How do we do for her?

NOTE Confidence: 0.9146245066666667

 $00:14:01.800 \longrightarrow 00:14:05.040$  Too well, not so well.

NOTE Confidence: 0.9146245066666667

 $00{:}14{:}05{.}040 \dashrightarrow 00{:}14{:}06{.}378$  This is the plot for her.

NOTE Confidence: 0.9146245066666667

 $00:14:06.380 \rightarrow 00:14:07.760 2/3$  plus or not three plus.

NOTE Confidence: 0.9146245066666667

 $00:14:07.760 \longrightarrow 00:14:09.340$  We're really good at that.

NOTE Confidence: 0.9146245066666667

 $00{:}14{:}09{.}340 \dashrightarrow 00{:}14{:}12{.}060$  But if you have a quartet of pathologists

NOTE Confidence: 0.9146245066666667

00:14:12.060 - 00:14:14.856 4 decide whether it's zero or not zero,

NOTE Confidence: 0.9146245066666667

00:14:14.860 --> 00:14:17.878 it's between 40 and 80 percent,

NOTE Confidence: 0.902744163636364

 $00{:}14{:}17{.}880 \dashrightarrow 00{:}14{:}19{.}665$ 85%. So this is a new method

NOTE Confidence: 0.902744163636364

 $00:14:19.665 \rightarrow 00:14:21.020$  to approach the analysis,

 $00:14:21.020 \longrightarrow 00:14:22.612$  to try to figure out how many we

NOTE Confidence: 0.902744163636364

 $00:14:22.612 \longrightarrow 00:14:24.382$  need and how many do we need to make

NOTE Confidence: 0.902744163636364

 $00:14:24.382 \rightarrow 00:14:26.016$  a new assay to make a good study.

NOTE Confidence: 0.902744163636364

 $00:14:26.020 \rightarrow 00:14:27.220$  Well, it's when it plateaus,

NOTE Confidence: 0.902744163636364

 $00:14:27.220 \longrightarrow 00:14:29.620$  so in this case we probably need 9 or 10.

NOTE Confidence: 0.902744163636364

 $00{:}14{:}29.620 \dashrightarrow 00{:}14{:}31.461$  And this case, no number is sufficient

NOTE Confidence: 0.902744163636364

 $00:14:31.461 \longrightarrow 00:14:33.617$  because it goes all the way down to the

NOTE Confidence: 0.902744163636364

 $00{:}14{:}33.617 \dashrightarrow 00{:}14{:}35.592$  baseline to tell ones from, not once.

NOTE Confidence: 0.902744163636364

 $00:14:35.592 \longrightarrow 00:14:38.262$  So the point is, I think that.

NOTE Confidence: 0.902744163636364

00:14:38.262 --> 00:14:40.386 I've I hope that I've convinced

NOTE Confidence: 0.902744163636364

 $00:14:40.386 \longrightarrow 00:14:42.619$  you that we need a new assay.

NOTE Confidence: 0.902744163636364

 $00{:}14{:}42.620 \dashrightarrow 00{:}14{:}44.475$  And so that's what we have done,

NOTE Confidence: 0.902744163636364

00:14:44.480 - 00:14:46.818 is propose a new assay that's measured,

NOTE Confidence: 0.902744163636364

 $00{:}14{:}46{.}820 \dashrightarrow 00{:}14{:}50{.}490$  not red. And so based on that.

NOTE Confidence: 0.902744163636364

 $00:14:50.490 \rightarrow 00:14:52.464$  We start, we started from the beginning

 $00:14:52.464 \rightarrow 00:14:54.347$  with cell lines and these cell lines

NOTE Confidence: 0.902744163636364

 $00:14:54.347 \rightarrow 00:14:56.390$  are all cell lines that are amplified,

NOTE Confidence: 0.902744163636364

00:14:56.390 --> 00:14:58.330 gene amplified and these cell

NOTE Confidence: 0.902744163636364

 $00:14:58.330 \longrightarrow 00:15:00.270$  lines are all gene express.

NOTE Confidence: 0.902744163636364

00:15:00.270 --> 00:15:00.848 Her too,

NOTE Confidence: 0.902744163636364

 $00{:}15{:}00{.}848 \dashrightarrow 00{:}15{:}02{.}582$  but are not gene amplified and

NOTE Confidence: 0.902744163636364

 $00:15:02.582 \rightarrow 00:15:04.646$  you can see when you plot them.

NOTE Confidence: 0.902744163636364

 $00{:}15{:}04.650 \dashrightarrow 00{:}15{:}06.876$  If you look with the current FDA

NOTE Confidence: 0.902744163636364

 $00{:}15{:}06.876 \dashrightarrow 00{:}15{:}08.863$  approved as say you can separate the

NOTE Confidence: 0.902744163636364

 $00:15:08.863 \rightarrow 00:15:11.290$  highs from the lows or the negatives,

NOTE Confidence: 0.902744163636364

 $00{:}15{:}11{.}290 \dashrightarrow 00{:}15{:}13{.}570$  but you can't stratify the negatives.

NOTE Confidence: 0.902744163636364

00:15:13.570 - 00:15:15.110 Whereas if you do the new assay

NOTE Confidence: 0.902744163636364

00:15:15.110 --> 00:15:16.848 high cut 10 times more antibody,

NOTE Confidence: 0.902744163636364

 $00:15:16.850 \rightarrow 00:15:18.122$  pretty simple new assay.

NOTE Confidence: 0.902744163636364

 $00:15:18.122 \rightarrow 00:15:20.382$  You can then stratify the low cell

NOTE Confidence: 0.902744163636364

 $00:15:20.382 \dashrightarrow 00:15:22.686$  lines and tell the zeros from the ones.

- NOTE Confidence: 0.902744163636364
- $00:15:22.690 \rightarrow 00:15:24.892$  Essentially if you were reading the
- NOTE Confidence: 0.902744163636364
- $00:15:24.892 \rightarrow 00:15:27.110$  cell lines but it was the wrong,
- NOTE Confidence: 0.902744163636364
- $00:15:27.110 \longrightarrow 00:15:28.952$  the wrong the current assay is
- NOTE Confidence: 0.902744163636364
- $00:15:28.952 \rightarrow 00:15:30.750$  the wrong tool for the job.
- NOTE Confidence: 0.902744163636364
- 00:15:30.750 00:15:35.556 Or as was said by a group in France.
- NOTE Confidence: 0.902744163636364
- $00{:}15{:}35{.}560 \dashrightarrow 00{:}15{:}37{.}558$  The current as say now FDA approved,
- NOTE Confidence: 0.902744163636364
- $00:15:37.560 \longrightarrow 00:15:39.570$  is like weighing mice on a
- NOTE Confidence: 0.902744163636364
- $00:15:39.570 \longrightarrow 00:15:40.575$  scale for elephants.
- NOTE Confidence: 0.902744163636364
- $00{:}15{:}40.580 \dashrightarrow 00{:}15{:}42.540$  And I think this is really good
- NOTE Confidence: 0.902744163636364
- $00:15:42.540 \longrightarrow 00:15:43.941$  because everybody gets this if
- NOTE Confidence: 0.902744163636364
- $00:15:43.941 \rightarrow 00:15:45.459$  you have a skill for elephants,
- NOTE Confidence: 0.902744163636364
- $00{:}15{:}45{.}460 \dashrightarrow 00{:}15{:}47{.}722$  it doesn't work for weighing mice
- NOTE Confidence: 0.902744163636364
- $00:15:47.722 \dashrightarrow 00:15:50.320$  and it's all about dynamic range.
- NOTE Confidence: 0.902744163636364
- $00{:}15{:}50{.}320 \dashrightarrow 00{:}15{:}52{.}308$  So here's the assay we did we
- NOTE Confidence: 0.902744163636364
- $00{:}15{:}52{.}308 \dashrightarrow 00{:}15{:}54{.}219$  invented and this is to have
- NOTE Confidence: 0.902744163636364

 $00:15:54.219 \longrightarrow 00:15:56.339$  a a series of cell lines and then

NOTE Confidence: 0.902744163636364

00:15:56.339 --> 00:15:58.327 just do like a Bradford assay like

NOTE Confidence: 0.902744163636364

 $00:15:58.327 \longrightarrow 00:15:59.855$  we all did in college chemistry

NOTE Confidence: 0.902744163636364

00:15:59.855 --> 00:16:01.919 for where we make a standard curve.

NOTE Confidence: 0.902744163636364

00:16:01.920 --> 00:16:03.866 And we used our tissue microarray to

NOTE Confidence: 0.902744163636364

 $00:16:03.866 \longrightarrow 00:16:06.103$  make cell lines and with the help of NOTE Confidence: 0.902744163636364

 $00:16:06.103 \rightarrow 00:16:07.820$  array science made a standard curve.

NOTE Confidence: 0.902744163636364

 $00:16:07.820 \rightarrow 00:16:09.948$  And then with the help of Crotia we

NOTE Confidence: 0.902744163636364

 $00{:}16{:}09{.}948 \dashrightarrow 00{:}16{:}11{.}714$  figured out how many animals per

NOTE Confidence: 0.902744163636364

00:16:11.714 --> 00:16:13.839 microgram there were in each of these

NOTE Confidence: 0.902744163636364

 $00{:}16{:}13.839 \dashrightarrow 00{:}16{:}15.639$  cell lines and then converted that

NOTE Confidence: 0.902744163636364

 $00:16:15.639 \rightarrow 00:16:17.568$  using Q path to how many animals

NOTE Confidence: 0.902744163636364

 $00:16:17.568 \rightarrow 00:16:18.853$  per square millimeter there are.

NOTE Confidence: 0.902744163636364

 $00:16:18.860 \longrightarrow 00:16:20.540$  So now we have an assay.

NOTE Confidence: 0.902744163636364

 $00:16:20.540 \longrightarrow 00:16:22.298$  That can tell us animals per

NOTE Confidence: 0.902744163636364

 $00:16:22.298 \rightarrow 00:16:22.884$  square millimeter.

- NOTE Confidence: 0.902744163636364
- $00:16:22.890 \longrightarrow 00:16:24.090$  And like all assays,
- NOTE Confidence: 0.902744163636364
- $00:16:24.090 \longrightarrow 00:16:26.250$  it saturates when it gets too high.
- NOTE Confidence: 0.902744163636364
- $00:16:26.250 \longrightarrow 00:16:27.820$  So the amplified cases are
- NOTE Confidence: 0.902744163636364
- $00:16:27.820 \longrightarrow 00:16:29.810$  saturated and we can't use those.
- NOTE Confidence: 0.902744163636364
- $00:16:29.810 \longrightarrow 00:16:30.896$  But since we don't really care
- NOTE Confidence: 0.902744163636364
- $00:16:30.896 \longrightarrow 00:16:32.089$  about 2 plus and three plus,
- NOTE Confidence: 0.902744163636364
- $00:16:32.090 \rightarrow 00:16:34.290$  we got that pathologists can do just fine
- NOTE Confidence: 0.902744163636364
- $00:16:34.290 \longrightarrow 00:16:36.327$  in telling 3 plus from not three plus.
- NOTE Confidence: 0.902744163636364
- $00:16:36.330 \longrightarrow 00:16:38.625$  We need an assay to tell 0 from 1.
- NOTE Confidence: 0.902744163636364
- $00:16:38.630 \rightarrow 00:16:40.429$  And so that's this assay works fine.
- NOTE Confidence: 0.902744163636364
- $00:16:40.430 \longrightarrow 00:16:41.725$  If we get rid of these two,
- NOTE Confidence: 0.902744163636364
- $00:16:41.730 \longrightarrow 00:16:43.480$  we can now build a very nice
- NOTE Confidence: 0.902744163636364
- $00{:}16{:}43{.}480 \dashrightarrow 00{:}16{:}44{.}974$  standard curve that we can use
- NOTE Confidence: 0.902744163636364
- $00{:}16{:}44{.}974 \dashrightarrow 00{:}16{:}46{.}577$  as a linear assay and then assign
- NOTE Confidence: 0.838703284074074
- $00{:}16{:}46{.}634 \dashrightarrow 00{:}16{:}48{.}930$  each case and animals per square millimeter.
- NOTE Confidence: 0.838703284074074

 $00:16:48.930 \longrightarrow 00:16:50.550$  And so just to remind you.

NOTE Confidence: 0.838703284074074

 $00{:}16{:}50{.}550 \dashrightarrow 00{:}16{:}51{.}852$  I'm going to talk a little bit

NOTE Confidence: 0.838703284074074

 $00:16:51.852 \longrightarrow 00:16:52.860$  about limits of detection,

NOTE Confidence: 0.838703284074074

 $00:16:52.860 \longrightarrow 00:16:53.850$  limits of quantification,

NOTE Confidence: 0.838703284074074

 $00{:}16{:}53.850 \dashrightarrow 00{:}16{:}55.170$  and limits on linearity.

NOTE Confidence: 0.838703284074074

 $00{:}16{:}55{.}170 \dashrightarrow 00{:}16{:}57{.}290$  A little bit of essay terminology and we

NOTE Confidence: 0.838703284074074

 $00:16:57.290 \rightarrow 00:16:59.500$  and this is the range we want to be in,

NOTE Confidence: 0.838703284074074

 $00:16:59.500 \longrightarrow 00:17:00.319$  not this range,

NOTE Confidence: 0.838703284074074

 $00{:}17{:}00{.}319$  -->  $00{:}17{:}01{.}957$  which is what the saturation range,

NOTE Confidence: 0.838703284074074

 $00{:}17{:}01{.}960 \dashrightarrow 00{:}17{:}04{.}190$  which is what the current

NOTE Confidence: 0.838703284074074

 $00:17:04.190 \longrightarrow 00:17:05.636$  essay really focuses on.

NOTE Confidence: 0.838703284074074

 $00:17:05.636 \rightarrow 00:17:06.964$  Because really the current

NOTE Confidence: 0.838703284074074

 $00:17:06.964 \longrightarrow 00:17:08.919$  as say all you need to tell is.

NOTE Confidence: 0.838703284074074

 $00:17:08.920 \longrightarrow 00:17:10.620$  Is it saturated or not?

NOTE Confidence: 0.838703284074074

 $00{:}17{:}10.620 \dashrightarrow 00{:}17{:}12.144$  For the new as say we need

NOTE Confidence: 0.838703284074074

 $00:17:12.144 \longrightarrow 00:17:13.830$  to tell how much they have.

 $00:17:13.830 \rightarrow 00:17:17.278$  So here's our the current our standard curve.

NOTE Confidence: 0.838703284074074

 $00:17:17.280 \longrightarrow 00:17:18.750$  With the higher two as say and

NOTE Confidence: 0.838703284074074

 $00:17:18.750 \longrightarrow 00:17:20.358$  you can see there's two positives

NOTE Confidence: 0.838703284074074

 $00:17:20.358 \rightarrow 00:17:21.788$  and the rest are negative.

NOTE Confidence: 0.838703284074074

 $00:17:21.790 \longrightarrow 00:17:23.902$  So it works if you just want to

NOTE Confidence: 0.838703284074074

00:17:23.902 --> 00:17:25.578 tell amplified from non amplified,

NOTE Confidence: 0.838703284074074

 $00:17:25.580 \longrightarrow 00:17:27.300$  but what if you want to tell that

NOTE Confidence: 0.838703284074074

 $00:17:27.300 \longrightarrow 00:17:28.980$  low range so you can see that you

NOTE Confidence: 0.838703284074074

 $00{:}17{:}28{.}980 \dashrightarrow 00{:}17{:}30{.}625$  can see the full dynamic range with

NOTE Confidence: 0.838703284074074

00:17:30.625 --> 00:17:32.480 the new her two low as say antibody

NOTE Confidence: 0.838703284074074

 $00:17:32.480 \longrightarrow 00:17:34.290$  concentration or that what we're

NOTE Confidence: 0.838703284074074

 $00{:}17{:}34.290 \dashrightarrow 00{:}17{:}36.100$  calling high sensitivity HSV or

NOTE Confidence: 0.838703284074074

 $00:17:36.161 \rightarrow 00:17:37.855$  two you can see in that range.

NOTE Confidence: 0.838703284074074

 $00{:}17{:}37{.}860 \dashrightarrow 00{:}17{:}39{.}364$  So now we have to talk about a

NOTE Confidence: 0.838703284074074

 $00:17:39.364 \longrightarrow 00:17:40.689$  little bit of wonky stuff and

 $00:17:40.689 \rightarrow 00:17:42.039$  that is what are those things.

NOTE Confidence: 0.838703284074074

 $00:17:42.040 \longrightarrow 00:17:43.776$  So what is the limit of detection,

NOTE Confidence: 0.838703284074074

 $00{:}17{:}43.780 \dashrightarrow 00{:}17{:}45.136$  what is the limit of quantification

NOTE Confidence: 0.838703284074074

 $00:17:45.136 \longrightarrow 00:17:46.948$  or what is the limit of linearity.

NOTE Confidence: 0.838703284074074

 $00{:}17{:}46.950 \dashrightarrow 00{:}17{:}47.990$  So these are the definitions

NOTE Confidence: 0.838703284074074

 $00{:}17{:}47{.}990 \dashrightarrow 00{:}17{:}48{.}822$  and this is right.

NOTE Confidence: 0.838703284074074

00:17:48.830 --> 00:17:51.214 One of the FDA's handbook on how they

NOTE Confidence: 0.838703284074074

 $00:17:51.214 \rightarrow 00:17:53.028$  advise industry to do this and you

NOTE Confidence: 0.838703284074074

 $00{:}17{:}53.028 \dashrightarrow 00{:}17{:}54.915$  can see that the limit of detection

NOTE Confidence: 0.838703284074074

 $00{:}17{:}54{.}915 \dashrightarrow 00{:}17{:}56{.}943$  is the lowest concentration of the

NOTE Confidence: 0.838703284074074

 $00{:}17{:}56{.}943 \dashrightarrow 00{:}17{:}58{.}944$  analyte that can be detected but

NOTE Confidence: 0.838703284074074

 $00:17:58.944 \longrightarrow 00:18:00.930$  not but and reliably to strings

NOTE Confidence: 0.838703284074074

00:18:00.998 --> 00:18:02.848 from zero but not necessarily

NOTE Confidence: 0.838703284074074

 $00{:}18{:}02{.}848 \dashrightarrow 00{:}18{:}04{.}698$  quantified that is too low.

NOTE Confidence: 0.838703284074074

 $00{:}18{:}04.700 \dashrightarrow 00{:}18{:}06.572$  So what we really want is to know

NOTE Confidence: 0.838703284074074

 $00:18:06.572 \rightarrow 00:18:07.994$  the limit of quantification because
$00:18:07.994 \rightarrow 00:18:10.420$  then we can do it right every time.

NOTE Confidence: 0.838703284074074

 $00:18:10.420 \longrightarrow 00:18:12.240$  But we don't yet know how much

NOTE Confidence: 0.838703284074074

 $00:18:12.240 \longrightarrow 00:18:14.181$  her two is required to benefit

NOTE Confidence: 0.838703284074074

 $00:18:14.181 \rightarrow 00:18:16.377$  from trust who's mab drug stcan.

NOTE Confidence: 0.838703284074074

 $00{:}18{:}16{.}380 \dashrightarrow 00{:}18{:}17{.}913$  So we're going to measure all the

NOTE Confidence: 0.838703284074074

 $00:18:17.913 \rightarrow 00:18:19.638$  way down to beyond the limits of.

NOTE Confidence: 0.838703284074074

 $00{:}18{:}19.640 \dashrightarrow 00{:}18{:}22.241$  Our essay to to the LD and below and

NOTE Confidence: 0.838703284074074

 $00:18:22.241 \rightarrow 00:18:25.207$  see what we get and what we got is this.

NOTE Confidence: 0.838703284074074

00:18:25.210 --> 00:18:27.394 When we did it on tissue microarray we

NOTE Confidence: 0.838703284074074

 $00:18:27.394 \longrightarrow 00:18:29.587$  could see that the the zeros are blue,

NOTE Confidence: 0.838703284074074

 $00{:}18{:}29{.}590 \dashrightarrow 00{:}18{:}31{.}820$  the Reds are one, ones are red, the twos.

NOTE Confidence: 0.838703284074074

 $00{:}18{:}31{.}820 \dashrightarrow 00{:}18{:}33{.}605$  This is the pathologist read over here

NOTE Confidence: 0.838703284074074

 $00{:}18{:}33{.}605 \dashrightarrow 00{:}18{:}35{.}853$ 2 Plus is black and three plus is green,

NOTE Confidence: 0.838703284074074

 $00{:}18{:}35{.}860 \dashrightarrow 00{:}18{:}37{.}240$  and most of the Greens are

NOTE Confidence: 0.838703284074074

 $00:18:37.240 \longrightarrow 00:18:38.730$  above our limit of linearity.

 $00{:}18{:}38{.}730 \dashrightarrow 00{:}18{:}40{.}794$  But look at how many twos and ones

NOTE Confidence: 0.838703284074074

 $00{:}18{:}40.794 \dashrightarrow 00{:}18{:}42.607$  there are in this middle range.

NOTE Confidence: 0.838703284074074

 $00:18:42.610 \longrightarrow 00:18:43.890$  That would be called one.

NOTE Confidence: 0.838703284074074

 $00{:}18{:}43.890 \dashrightarrow 00{:}18{:}45.850$  And I think this is even further evidence

NOTE Confidence: 0.838703284074074

 $00{:}18{:}45{.}850 \dashrightarrow 00{:}18{:}47{.}790$  that we need a a quantitative assay.

NOTE Confidence: 0.838703284074074

 $00:18:47.790 \longrightarrow 00:18:49.170$  We need a measured assay,

NOTE Confidence: 0.838703284074074

 $00{:}18{:}49{.}170 \dashrightarrow 00{:}18{:}49{.}788$  not a red.

NOTE Confidence: 0.838703284074074

00:18:49.788 --> 00:18:49.994 Say,

NOTE Confidence: 0.838703284074074

 $00:18:49.994 \rightarrow 00:18:51.230$  in order to pick the right

NOTE Confidence: 0.838703284074074

 $00:18:51.279 \rightarrow 00:18:52.799$  patients for trastuzumab drugs,

NOTE Confidence: 0.838703284074074

 $00:18:52.800 \rightarrow 00:18:54.996$  tican and surprisingly there are some

NOTE Confidence: 0.838703284074074

00:18:54.996 - 00:18:57.400 patients most of whom were called 0,

NOTE Confidence: 0.838703284074074

 $00{:}18{:}57{.}400 \dashrightarrow 00{:}18{:}59{.}073$  but some were called one or two

NOTE Confidence: 0.838703284074074

 $00:18:59.073 \rightarrow 00:19:00.677$  that are actually below our limit

NOTE Confidence: 0.838703284074074

 $00{:}19{:}00{.}677 \dashrightarrow 00{:}19{:}02{.}345$  of quantification or even below our

NOTE Confidence: 0.838703284074074

 $00:19:02.345 \dashrightarrow 00:19:04.237$  limit of detection as I'll show later.

- NOTE Confidence: 0.838703284074074
- $00:19:04.240 \longrightarrow 00:19:06.360$  So then we did what you have to do in

 $00{:}19{:}06{.}419 \dashrightarrow 00{:}19{:}07{.}679$  a clear lab is did 40,

NOTE Confidence: 0.808515345625

 $00:19:07.680 \rightarrow 00:19:10.218$  you have to do 20 positives and 20 negatives

NOTE Confidence: 0.808515345625

00:19:10.218 --> 00:19:12.122 according to Fitzgibbons at all in order

NOTE Confidence: 0.808515345625

 $00:19:12.122 \dashrightarrow 00:19:14.059$  to bring your assay to the CLIA lab.

NOTE Confidence: 0.808515345625

 $00{:}19{:}14.060 \dashrightarrow 00{:}19{:}15.887$  But we don't have positives and negatives.

NOTE Confidence: 0.808515345625

 $00:19:15.890 \longrightarrow 00:19:16.980$  We have a continuous scale.

NOTE Confidence: 0.808515345625

 $00:19:16.980 \longrightarrow 00:19:18.764$  So we did 40 of them and these

NOTE Confidence: 0.808515345625

 $00:19:18.764 \longrightarrow 00:19:20.029$  are actual core biopsies.

NOTE Confidence: 0.808515345625

00:19:20.030 --> 00:19:21.620 Now they're not tissue microarrays,

NOTE Confidence: 0.808515345625

 $00:19:21.620 \longrightarrow 00:19:22.894$  but you can see the same thing.

NOTE Confidence: 0.808515345625

00:19:22.900 --> 00:19:24.839 There's a fair bit of Miss Assignment

NOTE Confidence: 0.808515345625

 $00{:}19{:}24.839 \dashrightarrow 00{:}19{:}26.639$  and in fact summarized here,

NOTE Confidence: 0.808515345625

 $00{:}19{:}26.640 \dashrightarrow 00{:}19{:}29.656$  you can see that there's zeros and ones,

NOTE Confidence: 0.808515345625

 $00{:}19{:}29.660 \dashrightarrow 00{:}19{:}32.204$  but there's a broad range of animals per

 $00:19:32.204 \rightarrow 00:19:33.937$  square millimeter for zeros and ones.

NOTE Confidence: 0.808515345625

 $00{:}19{:}33{.}940 \dashrightarrow 00{:}19{:}37{.}244$  And the two plus not amplified almost

NOTE Confidence: 0.808515345625

 $00:19:37.244 \longrightarrow 00:19:39.828$  in fact does overlap with the two

NOTE Confidence: 0.808515345625

 $00:19:39.828 \rightarrow 00:19:41.580$  plus amplifies and the three pluses,

NOTE Confidence: 0.808515345625

 $00:19:41.580 \rightarrow 00:19:44.716$  which we're good at and we're pretty tight.

NOTE Confidence: 0.808515345625

 $00:19:44.720 \longrightarrow 00:19:45.950$  So how many are there?

NOTE Confidence: 0.808515345625

 $00:19:45.950 \longrightarrow 00:19:47.942$  Well, in our first forty there

NOTE Confidence: 0.808515345625

 $00:19:47.942 \rightarrow 00:19:50.124$  was about 20% of the cases that

NOTE Confidence: 0.808515345625

 $00{:}19{:}50{.}124 \dashrightarrow 00{:}19{:}52{.}378$  appear to be below the limit of

NOTE Confidence: 0.808515345625

 $00{:}19{:}52{.}378 \dashrightarrow 00{:}19{:}54{.}418$  quantification for her two protein,

NOTE Confidence: 0.808515345625

 $00{:}19{:}54{.}420 \dashrightarrow 00{:}19{:}57{.}070$  but potentially present and as

NOTE Confidence: 0.808515345625

 $00:19:57.070 \longrightarrow 00:20:01.280$  target for a target for TDXD.

NOTE Confidence: 0.808515345625

00:20:01.280 --> 00:20:03.254 So just to summarize to this point,

NOTE Confidence: 0.808515345625

00:20:03.260 --> 00:20:05.987 about 70% of the cases have low her two

NOTE Confidence: 0.808515345625

 $00{:}20{:}05{.}987 \dashrightarrow 00{:}20{:}08{.}701$  defined as above the LQ and below the

NOTE Confidence: 0.808515345625

 $00:20:08.701 \rightarrow 00:20:11.000$  levels associated with gene amplification.

- NOTE Confidence: 0.808515345625
- $00{:}20{:}11.000 \dashrightarrow 00{:}20{:}12.908$  About 8 to 10% are below
- NOTE Confidence: 0.808515345625
- $00:20:12.908 \longrightarrow 00:20:14.840$  our LQ or even our LD.
- NOTE Confidence: 0.808515345625
- $00{:}20{:}14.840 \dashrightarrow 00{:}20{:}17.556$  It's probably about 6% below our LD.
- NOTE Confidence: 0.808515345625
- $00{:}20{:}17.560 \dashrightarrow 00{:}20{:}18.600$  Many of the cases that
- NOTE Confidence: 0.808515345625
- $00{:}20{:}18.600 \dashrightarrow 00{:}20{:}19.640$  are called her to zero,
- NOTE Confidence: 0.808515345625
- $00:20:19.640 \longrightarrow 00:20:21.440$  as many as 60% are in our studies,
- NOTE Confidence: 0.808515345625
- $00:20:21.440 \longrightarrow 00:20:23.310$  maybe 75% have detectable amounts
- NOTE Confidence: 0.808515345625
- $00:20:23.310 \longrightarrow 00:20:26.394$  of her too between 3 and 20 animals
- NOTE Confidence: 0.808515345625
- $00{:}20{:}26{.}394 \dashrightarrow 00{:}20{:}28{.}680$  and the quantitative her two asset
- NOTE Confidence: 0.808515345625
- $00{:}20{:}28.680 \dashrightarrow 00{:}20{:}31.207$  could be envisioned as a reflex tax.
- NOTE Confidence: 0.808515345625
- $00:20:31.210 \longrightarrow 00:20:33.196$  So that if you pathologist reads
- NOTE Confidence: 0.808515345625
- 00:20:33.196 --> 00:20:34.520 an IHC equals zero,
- NOTE Confidence: 0.808515345625
- $00:20:34.520 \longrightarrow 00:20:36.458$  they could then reflex to the
- NOTE Confidence: 0.808515345625
- $00{:}20{:}36{.}458 \dashrightarrow 00{:}20{:}38{.}595$  quantitative test and the same way we
- NOTE Confidence: 0.808515345625
- $00:20:38.595 \rightarrow 00:20:42.620$  reflex to fish today for A2 plus HC.
- NOTE Confidence: 0.808515345625

 $00:20:42.620 \longrightarrow 00:20:45.448$  OK, so that's the proposed new assay.

NOTE Confidence: 0.808515345625

 $00:20:45.450 \longrightarrow 00:20:46.899$  Now let's take it to the clinic.

NOTE Confidence: 0.808515345625

 $00:20:46.900 \longrightarrow 00:20:48.406$  So what's involved in the next

NOTE Confidence: 0.808515345625

 $00:20:48.406 \longrightarrow 00:20:50.040$  step of taking to the clinic?

NOTE Confidence: 0.808515345625

 $00{:}20{:}50{.}040 \dashrightarrow 00{:}20{:}51{.}440$  And I like to quote a colleague

NOTE Confidence: 0.808515345625

00:20:51.440 --> 00:20:52.796 of mine from Brigham and Women's

NOTE Confidence: 0.808515345625

 $00:20:52.796 \longrightarrow 00:20:54.448$  who said once you have the essay

NOTE Confidence: 0.808515345625

 $00:20:54.500 \rightarrow 00:20:55.820$  working in your research lab,

NOTE Confidence: 0.808515345625

 $00{:}20{:}55{.}820 \dashrightarrow 00{:}20{:}57{.}770$  you're 5% of the way there.

NOTE Confidence: 0.808515345625

 $00:20:57.770 \longrightarrow 00:20:59.048$  And I think that's really true.

NOTE Confidence: 0.808515345625

 $00{:}20{:}59{.}050 \dashrightarrow 00{:}21{:}00{.}930$  Now having brought this assay

NOTE Confidence: 0.808515345625

 $00{:}21{:}00{.}930 \dashrightarrow 00{:}21{:}03{.}338$  with hats off to Trish Gal who's

NOTE Confidence: 0.808515345625

 $00:21:03.338 \longrightarrow 00:21:05.450$  not here and has not left,

NOTE Confidence: 0.808515345625

 $00{:}21{:}05{.}450 \dashrightarrow 00{:}21{:}07{.}997$  Nay Chan who was in the audience and Reva

NOTE Confidence: 0.808515345625

 $00{:}21{:}07{.}997 \dashrightarrow 00{:}21{:}10{.}283$  come ova who have helped me to bring

NOTE Confidence: 0.808515345625

 $00:21:10.283 \rightarrow 00:21:12.470$  this assay to the clinical setting.

- NOTE Confidence: 0.808515345625
- $00:21:12.470 \longrightarrow 00:21:13.670$  So the things that you have
- NOTE Confidence: 0.808515345625
- 00:21:13.670 --> 00:21:14.950 to do are antibody titration,
- NOTE Confidence: 0.808515345625
- $00:21:14.950 \longrightarrow 00:21:16.582$  maximization of signal to
- NOTE Confidence: 0.808515345625
- $00:21:16.582 \rightarrow 00:21:17.806$  noise analytic validation.
- NOTE Confidence: 0.808515345625
- $00{:}21{:}17.810 \dashrightarrow 00{:}21{:}19.482$  I'll try to go through this stuff fast
- NOTE Confidence: 0.808515345625
- $00{:}21{:}19{.}482 \dashrightarrow 00{:}21{:}21{.}047$  because it's a little on the wonky side,
- NOTE Confidence: 0.808515345625
- 00:21:21.050 --> 00:21:22.604 performance accuracy, precision,
- NOTE Confidence: 0.808515345625
- 00:21:22.604 --> 00:21:24.676 sensitivity and specificity and
- NOTE Confidence: 0.808515345625
- 00:21:24.676 --> 00:21:26.230 serial core reproducibility.
- NOTE Confidence: 0.808515345625
- $00:21:26.230 \rightarrow 00:21:27.766$  And then how do we tell our colleagues?
- NOTE Confidence: 0.808515345625
- $00:21:27.770 \longrightarrow 00:21:29.180$  What do we tell the oncologists?
- NOTE Confidence: 0.808515345625
- $00{:}21{:}29{.}180 \dashrightarrow 00{:}21{:}30{.}584$  And then so the reporting is
- NOTE Confidence: 0.808515345625
- $00:21:30.584 \longrightarrow 00:21:31.840$  part of this as well.
- NOTE Confidence: 0.808515345625
- $00:21:31.840 \longrightarrow 00:21:32.644$  So first of all,
- NOTE Confidence: 0.808515345625
- $00{:}21{:}32{.}644 \dashrightarrow 00{:}21{:}34{.}117$  we looked at the signal to noise
- NOTE Confidence: 0.808515345625

 $00:21:34.117 \longrightarrow 00:21:35.594$  and you can see that the peak

NOTE Confidence: 0.808515345625

00:21:35.594 --> 00:21:37.025 signal to noise is at 1 microgram

NOTE Confidence: 0.808515345625

00:21:37.025 --> 00:21:38.331 per mil for a new antibody.

NOTE Confidence: 0.808515345625

 $00:21:38.331 \longrightarrow 00:21:40.036$  This is a new higher

NOTE Confidence: 0.808515345625

 $00:21:40.036 \longrightarrow 00:21:41.400$  sensitivity antibody for her

NOTE Confidence: 0.8169936435

 $00{:}21{:}41{.}463 \dashrightarrow 00{:}21{:}42{.}993$  too than the one that's

NOTE Confidence: 0.8169936435

 $00:21:42.993 \longrightarrow 00:21:44.523$  currently used in the clinic.

NOTE Confidence: 0.8169936435

 $00:21:44.530 \longrightarrow 00:21:46.203$  And we took and we picked the

NOTE Confidence: 0.8169936435

 $00{:}21{:}46{.}203 \dashrightarrow 00{:}21{:}47{.}420$  concentration with the maximal signal

NOTE Confidence: 0.8169936435

 $00{:}21{:}47{.}420 \dashrightarrow 00{:}21{:}49{.}220$  to noise and then we looked at the

NOTE Confidence: 0.8169936435

 $00{:}21{:}49{.}271 \dashrightarrow 00{:}21{:}51{.}017$  accuracy and our accuracy isn't great,

NOTE Confidence: 0.8169936435

 $00:21:51.020 \rightarrow 00:21:53.666$  it's only 87%. Why is that?

NOTE Confidence: 0.8169936435

 $00{:}21{:}53.670 \dashrightarrow 00{:}21{:}55.932$  That's because we're more sensitive than

NOTE Confidence: 0.8169936435

 $00:21:55.932 \longrightarrow 00:21:58.579$  the status quo assay which we had to

NOTE Confidence: 0.8169936435

 $00{:}21{:}58{.}579$  -->  $00{:}22{:}01{.}648$  compare it to which was HC012 and three.

NOTE Confidence: 0.8169936435

 $00:22:01.648 \longrightarrow 00:22:04.565$  But overall we have quite a quite

- NOTE Confidence: 0.8169936435
- $00:22:04.565 \longrightarrow 00:22:06.723$  good concordance especially in the end

 $00:22:06.723 \rightarrow 00:22:08.984$  and more resolution in the low range.

NOTE Confidence: 0.8169936435

 $00:22:08.990 \longrightarrow 00:22:11.390$  And then our intra and intra

NOTE Confidence: 0.8169936435

 $00:22:11.390 \rightarrow 00:22:13.450$  assay precision is quite high,

NOTE Confidence: 0.8169936435

 $00:22:13.450 \longrightarrow 00:22:15.178 \ 10\%$  sounds like it might not be great.

NOTE Confidence: 0.8169936435

 $00:22:15.180 \rightarrow 00:22:16.884$  To interact assay precision and actually

NOTE Confidence: 0.8169936435

 $00:22:16.884 \rightarrow 00:22:18.858$  the essay that we just bridged to,

NOTE Confidence: 0.8169936435

 $00:22:18.860 \longrightarrow 00:22:20.308$  we're now under 10%,

NOTE Confidence: 0.8169936435

 $00:22:20.308 \longrightarrow 00:22:22.118$  but it's acceptable and the

NOTE Confidence: 0.8169936435

00:22:22.118 --> 00:22:23.629 intra assay precision,

NOTE Confidence: 0.8169936435

 $00:22:23.630 \longrightarrow 00:22:25.640$  this means to calculate the precision

NOTE Confidence: 0.8169936435

 $00:22:25.640 \longrightarrow 00:22:27.363$  three slides run on separate

NOTE Confidence: 0.8169936435

 $00:22:27.363 \longrightarrow 00:22:29.277$  trays at the same machine is,

NOTE Confidence: 0.8169936435

 $00:22:29.280 \longrightarrow 00:22:30.392$  is, is about 5%.

NOTE Confidence: 0.8169936435

 $00:22:30.392 \longrightarrow 00:22:32.519$  So these are where we want to be.

 $00:22:32.520 \rightarrow 00:22:35.022$  Our sensitivity compared to the historical

NOTE Confidence: 0.8169936435

 $00:22:35.022 \rightarrow 00:22:38.520$  essay as 100% and our specificity is 84%.

NOTE Confidence: 0.8169936435

 $00:22:38.520 \rightarrow 00:22:39.840$  Why is our specificity low?

NOTE Confidence: 0.8169936435

 $00{:}22{:}39{.}840 \dashrightarrow 00{:}22{:}42{.}025$  Because we're more sensitive and

NOTE Confidence: 0.8169936435

 $00{:}22{:}42.025 \dashrightarrow 00{:}22{:}44.721$  so we call cases positive that

NOTE Confidence: 0.8169936435

 $00:22:44.721 \rightarrow 00:22:46.856$  we're called negative by IHC.

NOTE Confidence: 0.8169936435

 $00:22:46.860 \longrightarrow 00:22:48.770$  So here's the proposed clinical

NOTE Confidence: 0.8169936435

 $00{:}22{:}48.770 \dashrightarrow 00{:}22{:}51.028$  future work workflow and this is

NOTE Confidence: 0.8169936435

00:22:51.028 --> 00:22:52.974 what we're doing now which is we

NOTE Confidence: 0.8169936435

 $00{:}22{:}52{.}974 \dashrightarrow 00{:}22{:}54{.}758$  have we get the labs come to this

NOTE Confidence: 0.8169936435

00:22:54.758 --> 00:22:56.969 lab that I've called the qutab lab

NOTE Confidence: 0.8169936435

 $00{:}22{:}56{.}969 \dashrightarrow 00{:}22{:}58{.}481$  quantitative diagnostics and an atomic

NOTE Confidence: 0.8169936435

 $00{:}22{:}58{.}481 \dashrightarrow 00{:}23{:}00{.}283$  pathology which is a new lab which

NOTE Confidence: 0.8169936435

 $00:23:00.283 \rightarrow 00:23:01.870$  is now open and open for business.

NOTE Confidence: 0.8169936435

00:23:01.870 - 00:23:03.935 And we've now begun to do this.

NOTE Confidence: 0.8169936435

 $00:23:03.940 \rightarrow 00:23:06.500$  This is and this is qdap essay #1,

- NOTE Confidence: 0.8169936435
- $00:23:06.500 \rightarrow 00:23:07.956$  the high sensitivity here.

00:23:07.956 --> 00:23:08.320 Two,

NOTE Confidence: 0.8169936435

 $00{:}23{:}08{.}320 \dashrightarrow 00{:}23{:}09{.}881$  we batched the stains and do them

NOTE Confidence: 0.8169936435

 $00:23:09.881 \longrightarrow 00:23:11.744$  in our like a bond stainer so that

NOTE Confidence: 0.8169936435

00:23:11.744 --> 00:23:13.196 they're done in an auto stainer

NOTE Confidence: 0.8169936435

00:23:13.196 - 00:23:14.744 and then we read them originally

NOTE Confidence: 0.8169936435

 $00:23:14.744 \rightarrow 00:23:16.594$  in some old like legacy hardware.

NOTE Confidence: 0.8169936435

00:23:16.594 --> 00:23:18.384 But now we're using this,

NOTE Confidence: 0.8169936435

 $00:23:18.390 \rightarrow 00:23:20.686$  we just recently completed the bridge study,

NOTE Confidence: 0.8169936435

00:23:20.690 --> 00:23:21.858 although our license holder

NOTE Confidence: 0.8169936435

00:23:21.858 --> 00:23:23.026 hasn't signed off yet,

NOTE Confidence: 0.8169936435

 $00{:}23{:}23{.}030 \dashrightarrow 00{:}23{:}26{.}046$  he will see it shortly and uses a

NOTE Confidence: 0.8169936435

 $00{:}23{:}26.046 \dashrightarrow 00{:}23{:}27.506$  much more high throughput device.

NOTE Confidence: 0.8169936435

 $00{:}23{:}27{.}510$  -->  $00{:}23{:}29{.}449$  Instead of an hour this machine would

NOTE Confidence: 0.8169936435

 $00{:}23{:}29{.}449 \dashrightarrow 00{:}23{:}31{.}590$  take about four minutes to scan a slide.

 $00:23:31.590 \rightarrow 00:23:33.557$  So we wanted to update our technology

NOTE Confidence: 0.8169936435

00:23:33.557 --> 00:23:35.364 a little bit and then we signed

NOTE Confidence: 0.8169936435

 $00{:}23{:}35{.}364 \dashrightarrow 00{:}23{:}37{.}450$  it out and Co path as a procedure.

NOTE Confidence: 0.8169936435

 $00{:}23{:}37{.}450 \dashrightarrow 00{:}23{:}39{.}284$  And so it ultimately makes it to

NOTE Confidence: 0.8169936435

 $00{:}23{:}39{.}284 \dashrightarrow 00{:}23{:}41{.}409$  epic and and clinicians can see it,

NOTE Confidence: 0.8169936435

 $00:23:41.410 \longrightarrow 00:23:42.790$  this is what it looks like.

NOTE Confidence: 0.8169936435

 $00{:}23{:}42.790 \dashrightarrow 00{:}23{:}44.288$  The pathologist has to pick a region.

NOTE Confidence: 0.8169936435

 $00:23:44.290 \rightarrow 00:23:45.890$  So we're actually not measuring

NOTE Confidence: 0.8169936435

 $00{:}23{:}45{.}890 \dashrightarrow 00{:}23{:}47{.}170$  the entire core biopsy.

NOTE Confidence: 0.8169936435

 $00{:}23{:}47{.}170 \dashrightarrow 00{:}23{:}49{.}114$  We're measuring a region that is

NOTE Confidence: 0.8169936435

 $00{:}23{:}49{.}114 \dashrightarrow 00{:}23{:}50{.}783$  quote UN quote representative and

NOTE Confidence: 0.8169936435

 $00{:}23{:}50.783 \dashrightarrow 00{:}23{:}52.059$  that representative region is

NOTE Confidence: 0.8169936435

 $00{:}23{:}52{.}059 \dashrightarrow 00{:}23{:}53{.}335$  then looks like this.

NOTE Confidence: 0.8169936435

 $00{:}23{:}53{.}340 \dashrightarrow 00{:}23{:}54{.}999$  This is actually not a brown stain

NOTE Confidence: 0.8169936435

 $00{:}23{:}54{.}999 \dashrightarrow 00{:}23{:}57{.}074$  but a pseudo IHC which it shows the

NOTE Confidence: 0.8169936435

 $00:23:57.074 \rightarrow 00:23:58.748$  pathologist what they what it looked

 $00:23:58.748 \rightarrow 00:24:00.596$  like and then the pathologist actually

NOTE Confidence: 0.8169936435

00:24:00.596 --> 00:24:02.844 sees the number of fields of view,

NOTE Confidence: 0.8169936435

 $00:24:02.844 \longrightarrow 00:24:06.003$  in this case 23 and the in this case

NOTE Confidence: 0.8169936435

 $00{:}24{:}06{.}003 \dashrightarrow 00{:}24{:}08{.}860$  the rare sight score in this case was

NOTE Confidence: 0.8169936435

 $00:24:08.860 \rightarrow 00:24:10.540$  15.4 animals per square millimeter.

NOTE Confidence: 0.8169936435

 $00{:}24{:}10.540 \dashrightarrow 00{:}24{:}12.596$  So that will be included in the report.

NOTE Confidence: 0.8169936435

00:24:12.600 --> 00:24:15.096 We'd say 15.4 animals require millimeter.

NOTE Confidence: 0.8169936435

 $00:24:15.100 \longrightarrow 00:24:17.176$  We don't know what that means.

NOTE Confidence: 0.8169936435

00:24:17.180 --> 00:24:17.648 I mean,

NOTE Confidence: 0.8169936435

 $00{:}24{:}17.648 \dashrightarrow 00{:}24{:}19.052$  we do know that it's detectable

NOTE Confidence: 0.8169936435

 $00{:}24{:}19.052 \dashrightarrow 00{:}24{:}19.520$  and then

NOTE Confidence: 0.830076910416667

 $00{:}24{:}19{.}570 \dashrightarrow 00{:}24{:}21{.}594$  we can give a choice in our interpretation

NOTE Confidence: 0.830076910416667

 $00{:}24{:}21{.}594 \dashrightarrow 00{:}24{:}23{.}567$  that it's positive for expression high.

NOTE Confidence: 0.830076910416667

 $00{:}24{:}23.570 \dashrightarrow 00{:}24{:}26.266$  That is, it's above our limit of linearity

NOTE Confidence: 0.830076910416667

 $00:24:26.266 \rightarrow 00:24:27.710$  positive expression intermediate,

 $00:24:27.710 \longrightarrow 00:24:29.726$  which means that it's like a one

NOTE Confidence: 0.830076910416667

00:24:29.726 --> 00:24:31.818 or A2 positive for expression low,

NOTE Confidence: 0.830076910416667

 $00:24:31.820 \longrightarrow 00:24:33.284$  which means it's.

NOTE Confidence: 0.830076910416667

 $00:24:33.284 \rightarrow 00:24:36.700$  Present, but it might not be reproducible.

NOTE Confidence: 0.830076910416667

 $00:24:36.700 \longrightarrow 00:24:39.045$  That is, it's above our LOD but

NOTE Confidence: 0.830076910416667

00:24:39.045 --> 00:24:40.750 not necessarily above our LOQ

NOTE Confidence: 0.830076910416667

 $00:24:40.750 \rightarrow 00:24:42.646$  and then negative below the LOD.

NOTE Confidence: 0.830076910416667

 $00:24:42.650 \rightarrow 00:24:45.210$  And so these are the reports that we'll

NOTE Confidence: 0.830076910416667

 $00{:}24{:}45{.}210 \dashrightarrow 00{:}24{:}48{.}115$  issue as as we start to receive specimens.

NOTE Confidence: 0.830076910416667

 $00:24:48.120 \rightarrow 00:24:51.234$  So far we've received a grand total of two.

NOTE Confidence: 0.830076910416667

 $00{:}24{:}51{.}240 \dashrightarrow 00{:}24{:}53{.}632$  We hope that after this talk and may be

NOTE Confidence: 0.830076910416667

 $00:24:53.632 \longrightarrow 00:24:56.501$  in the future and certainly in the more

NOTE Confidence: 0.830076910416667

 $00{:}24{:}56{.}501 \dashrightarrow 00{:}24{:}58{.}970$  distant future when we know how much.

NOTE Confidence: 0.830076910416667

 $00:24:58.970 \rightarrow 00:25:01.550$  Is necessary for patients to respond.

NOTE Confidence: 0.830076910416667

 $00:25:01.550 \rightarrow 00:25:03.386$  We hope that this essay will

NOTE Confidence: 0.830076910416667

 $00:25:03.386 \longrightarrow 00:25:04.304$  gain some traction.

 $00:25:04.310 \rightarrow 00:25:07.424$  So our vision we currently offer HSR 2 in

NOTE Confidence: 0.830076910416667

 $00{:}25{:}07{.}424 \dashrightarrow 00{:}25{:}09{.}952$  the QDAP lab test must be requested by an

NOTE Confidence: 0.830076910416667

 $00{:}25{:}09{.}952 \dashrightarrow 00{:}25{:}11{.}469$  on cologist and the patients are billed.

NOTE Confidence: 0.830076910416667

 $00{:}25{:}11.470 \dashrightarrow 00{:}25{:}13.790$  If the test is requested by an oncologist,

NOTE Confidence: 0.830076910416667

 $00{:}25{:}13.790 \dashrightarrow 00{:}25{:}16.254$  there are I CD9 codes for all

NOTE Confidence: 0.830076910416667

 $00:25:16.254 \rightarrow 00:25:17.860$  the stuff we're doing.

NOTE Confidence: 0.830076910416667

 $00{:}25{:}17.860 \dashrightarrow 00{:}25{:}20.436$  We began a prospective study on all

NOTE Confidence: 0.830076910416667

 $00{:}25{:}20{.}436 \dashrightarrow 00{:}25{:}23{.}317$  breast biopsies so that we have data of

NOTE Confidence: 0.830076910416667

 $00{:}25{:}23{.}317 \dashrightarrow 00{:}25{:}25{.}788$  a year's worth of prospective data and

NOTE Confidence: 0.830076910416667

 $00{:}25{:}25{.}788 \dashrightarrow 00{:}25{:}28{.}224$  we're about seven months into it now.

NOTE Confidence: 0.830076910416667

 $00{:}25{:}28{.}230 \dashrightarrow 00{:}25{:}29{.}915$  We offer the essay coalitions

NOTE Confidence: 0.830076910416667

 $00{:}25{:}29{.}915 \dashrightarrow 00{:}25{:}32{.}715$  from to Yale or elsewhere who want

NOTE Confidence: 0.830076910416667

00:25:32.715 --> 00:25:33.759 quantitative information,

NOTE Confidence: 0.830076910416667

 $00{:}25{:}33{.}760 \dashrightarrow 00{:}25{:}35{.}580$  but only two so far to date.

NOTE Confidence: 0.830076910416667

 $00{:}25{:}35{.}580 \dashrightarrow 00{:}25{:}37{.}500$  And then the discussions of the

 $00:25:37.500 \longrightarrow 00:25:38.460$  license we will.

NOTE Confidence: 0.830076910416667

 $00:25:38.460 \longrightarrow 00:25:40.042$  What we hope to happen is ultimately

NOTE Confidence: 0.830076910416667

 $00:25:40.042 \longrightarrow 00:25:41.896$  it won't just be yell that can do this,

NOTE Confidence: 0.830076910416667

 $00:25:41.900 \longrightarrow 00:25:43.377$  but we'll license it to some of

NOTE Confidence: 0.830076910416667

 $00{:}25{:}43{.}377 \dashrightarrow 00{:}25{:}44{.}915$  the big lab companies that provide

NOTE Confidence: 0.830076910416667

 $00{:}25{:}44{.}915 \dashrightarrow 00{:}25{:}46{.}619$  them the bulk of the service.

NOTE Confidence: 0.830076910416667

 $00:25:46.620 \longrightarrow 00:25:48.005$  It's interesting to know and

NOTE Confidence: 0.830076910416667

 $00:25:48.005 \rightarrow 00:25:49.113$  interesting to me anyway,

NOTE Confidence: 0.830076910416667

 $00:25:49.120 \longrightarrow 00:25:51.640$  that only 15% of lab tests in the

NOTE Confidence: 0.830076910416667

 $00:25:51.640 \rightarrow 00:25:54.399$  US are provided by academic labs.

NOTE Confidence: 0.830076910416667

 $00:25:54.400 \longrightarrow 00:25:57.736$  The other 85% are provided by private labs.

NOTE Confidence: 0.830076910416667

 $00:25:57.740 \longrightarrow 00:25:59.000$  And so clearly if we want to.

NOTE Confidence: 0.830076910416667

 $00{:}25{:}59{.}000 \dashrightarrow 00{:}26{:}02{.}378$  Have this effect patients around

NOTE Confidence: 0.830076910416667

 $00{:}26{:}02{.}378 \dashrightarrow 00{:}26{:}04{.}646$  the world and be useful and needs

NOTE Confidence: 0.830076910416667

 $00:26:04.646 \longrightarrow 00:26:07.361$  to make it into private labs and

NOTE Confidence: 0.830076910416667

 $00:26:07.361 \longrightarrow 00:26:08.909$  those discussions are beginning.

 $00{:}26{:}08{.}910 \dashrightarrow 00{:}26{:}11{.}770$  So the last thing I want to talk about is

NOTE Confidence: 0.830076910416667

 $00:26:11.770 \longrightarrow 00:26:14.650$  the precision versus persuasion medicine.

NOTE Confidence: 0.830076910416667

 $00{:}26{:}14.650 \dashrightarrow 00{:}26{:}16.900$  And so our original envision for

NOTE Confidence: 0.830076910416667

 $00{:}26{:}16{.}900 \dashrightarrow 00{:}26{:}19{.}590$  this essay was that we would need

NOTE Confidence: 0.830076910416667

 $00:26:19.590 \longrightarrow 00:26:21.412$  to adjudicate the IHC's equal 0.

NOTE Confidence: 0.830076910416667

 $00{:}26{:}21.412 \dashrightarrow 00{:}26{:}23.628$  And what we would do is we would get

NOTE Confidence: 0.830076910416667

 $00{:}26{:}23.628 \dashrightarrow 00{:}26{:}25.684$  all the HC equals zero and we would

NOTE Confidence: 0.830076910416667

 $00:26:25.746 \longrightarrow 00:26:27.986$  measure them and then we tell you if

NOTE Confidence: 0.830076910416667

 $00{:}26{:}27{.}986 \dashrightarrow 00{:}26{:}29{.}590$  you're above the limit of detection

NOTE Confidence: 0.830076910416667

 $00:26:29.590 \longrightarrow 00:26:31.150$  or above the limit of response.

NOTE Confidence: 0.830076910416667

 $00{:}26{:}31{.}150 \dashrightarrow 00{:}26{:}33{.}126$  We don't know the limit of response yet.

NOTE Confidence: 0.830076910416667

 $00{:}26{:}33.130 \dashrightarrow 00{:}26{:}34.887$  Someday we will and I'll show you

NOTE Confidence: 0.830076910416667

 $00{:}26{:}34.887 \dashrightarrow 00{:}26{:}36.388$  how we intend to get there.

NOTE Confidence: 0.830076910416667

 $00{:}26{:}36{.}390 \dashrightarrow 00{:}26{:}37{.}692$  But right now we don't know the

NOTE Confidence: 0.830076910416667

 $00:26:37.692 \longrightarrow 00:26:38.440$  limit of response but.

 $00{:}26{:}38{.}440 \dashrightarrow 00{:}26{:}40{.}421$  You would take all the cases that

NOTE Confidence: 0.830076910416667

 $00{:}26{:}40{.}421 \dashrightarrow 00{:}26{:}42{.}416$  were called HC0 and maybe the cases

NOTE Confidence: 0.830076910416667

 $00{:}26{:}42.416$  -->  $00{:}26{:}44.569$  that were called HC One and do that.

NOTE Confidence: 0.830076910416667

 $00:26:44.570 \rightarrow 00:26:46.256$  But something happened in the last

NOTE Confidence: 0.830076910416667

 $00{:}26{:}46.256 \dashrightarrow 00{:}26{:}48.170$  three or four months and I haven't

NOTE Confidence: 0.830076910416667

 $00:26:48.170 \longrightarrow 00:26:49.634$  been able to document it yet,

NOTE Confidence: 0.830076910416667

00:26:49.640 --> 00:26:51.530 probably because it's not mature enough,

NOTE Confidence: 0.830076910416667

 $00:26:51.530 \rightarrow 00:26:55.370$  but suddenly the IHC equals zero is rare.

NOTE Confidence: 0.830076910416667

 $00{:}26{:}55{.}370 \dashrightarrow 00{:}26{:}57{.}150$  And that's because pathologists

NOTE Confidence: 0.830076910416667

 $00:26:57.150 \longrightarrow 00:26:58.485$  are people too.

NOTE Confidence: 0.830076910416667

 $00{:}26{:}58{.}490 \dashrightarrow 00{:}26{:}59{.}878$  Pathologists sometimes might be

NOTE Confidence: 0.830076910416667

 $00{:}26{:}59{.}878 \dashrightarrow 00{:}27{:}01{.}960$  a little more lenient on what

NOTE Confidence: 0.795286742857143

 $00:27:02.026 \rightarrow 00:27:04.098$  they call IHC one and this code

NOTE Confidence: 0.795286742857143

00:27:04.098 --> 00:27:05.334 called Sympathy vote because

NOTE Confidence: 0.795286742857143

 $00:27:05.334 \rightarrow 00:27:07.329$  then they can get this new drug.

NOTE Confidence: 0.795286742857143

 $00:27:07.330 \rightarrow 00:27:09.087$  Here are real quotes that I've heard.

- NOTE Confidence: 0.795286742857143
- $00:27:09.090 \longrightarrow 00:27:11.736$  I won't quote the people because to
- NOTE Confidence: 0.795286742857143
- $00:27:11.736 \longrightarrow 00:27:14.347$  not embarrass them or give them credit,
- NOTE Confidence: 0.795286742857143
- $00:27:14.350 \longrightarrow 00:27:15.540$  but here's a real quote.
- NOTE Confidence: 0.795286742857143
- $00:27:15.540 \longrightarrow 00:27:16.413$  Hi doctor pathologist.
- NOTE Confidence: 0.795286742857143
- 00:27:16.413 --> 00:27:18.159 So I see you called Missus
- NOTE Confidence: 0.795286742857143
- 00:27:18.159 --> 00:27:19.389 X's biopsy IHC zero.
- NOTE Confidence: 0.795286742857143
- $00:27:19.390 \longrightarrow 00:27:20.716$  That means I'm going to have
- NOTE Confidence: 0.795286742857143
- $00:27:20.716 \longrightarrow 00:27:22.120$  to offer her brain radiation.
- NOTE Confidence: 0.795286742857143
- $00{:}27{:}22.120 \dashrightarrow 00{:}27{:}24.360$  Are you sure it's not H sequels one?
- NOTE Confidence: 0.795286742857143
- 00:27:24.360 --> 00:27:25.809 Then I could give her her and her two.
- NOTE Confidence: 0.86010612
- 00:27:27.950 --> 00:27:30.070 Should I go look at that slide again?
- NOTE Confidence: 0.86010612
- $00{:}27{:}30.070 \dashrightarrow 00{:}27{:}32.086$  Does that mean that my first view
- NOTE Confidence: 0.86010612
- $00:27:32.086 \longrightarrow 00:27:34.060$  of that slide was not accurate?
- NOTE Confidence: 0.86010612
- $00{:}27{:}34.060 \dashrightarrow 00{:}27{:}36.316$  Or was it accurate and may be
- NOTE Confidence: 0.86010612
- $00:27:36.316 \rightarrow 00:27:38.700$  I should change my diagnosis?
- NOTE Confidence: 0.86010612

- $00:27:38.700 \longrightarrow 00:27:40.652$  Because I'm persuaded that
- NOTE Confidence: 0.86010612
- $00{:}27{:}40.652 \dashrightarrow 00{:}27{:}43.092$  that's better for the patient.
- NOTE Confidence: 0.86010612
- $00{:}27{:}43.100 \dashrightarrow 00{:}27{:}44.908$  I'm not sure that's a great idea from
- NOTE Confidence: 0.86010612
- 00:27:44.908 --> 00:27:46.819 West Coast director of pathology service.
- NOTE Confidence: 0.86010612
- $00:27:46.820 \longrightarrow 00:27:48.405$  Yeah, we don't have many
- NOTE Confidence: 0.86010612
- 00:27:48.405 --> 00:27:49.673 IHC's equal 0 anymore.
- NOTE Confidence: 0.86010612
- 00:27:49.680 --> 00:27:51.700 And from a Midwestern oncologist,
- NOTE Confidence: 0.86010612
- $00:27:51.700 \rightarrow 00:27:53.152$  I'm not seeing the response rates
- NOTE Confidence: 0.86010612
- $00{:}27{:}53.152 \dashrightarrow 00{:}27{:}54.744$  and in her two patients that
- NOTE Confidence: 0.86010612
- $00{:}27{:}54{.}744 \dashrightarrow 00{:}27{:}56{.}448$  they saw in the clinical trial.
- NOTE Confidence: 0.86010612
- $00{:}27{:}56{.}450 \dashrightarrow 00{:}27{:}59{.}221$  They're getting a lot of IHC zeros and
- NOTE Confidence: 0.86010612
- $00{:}27{:}59{.}221 \dashrightarrow 00{:}28{:}01{.}087$  maybe IHC zeros really don't respond.
- NOTE Confidence: 0.86010612
- $00{:}28{:}01{.}090 \dashrightarrow 00{:}28{:}03{.}570$  We know that eight to 10% of the
- NOTE Confidence: 0.86010612
- $00{:}28{:}03{.}570 \dashrightarrow 00{:}28{:}05{.}670$  cases really don't express any target
- NOTE Confidence: 0.86010612
- $00:28:05.670 \longrightarrow 00:28:07.710$  and this is a targeted therapy.
- NOTE Confidence: 0.86010612
- 00:28:07.710 --> 00:28:09.070 I mean we don't definitively

- NOTE Confidence: 0.86010612
- $00:28:09.070 \longrightarrow 00:28:10.430$  know how the drug works,

 $00{:}28{:}10{.}430 \dashrightarrow 00{:}28{:}12{.}509$  but we think it's a targeted the rapy.

NOTE Confidence: 0.86010612

 $00:28:12.510 \longrightarrow 00:28:13.572$  After all,

NOTE Confidence: 0.86010612

 $00:28:13.572 \rightarrow 00:28:16.227$  it's trastuzumab conjugated to toxins.

NOTE Confidence: 0.86010612

 $00:28:16.230 \longrightarrow 00:28:18.120$  So what's happened is that really

NOTE Confidence: 0.86010612

 $00{:}28{:}18{.}120 \dashrightarrow 00{:}28{:}20{.}568$  now we need to adjudicate the one

NOTE Confidence: 0.86010612

 $00:28:20.568 \rightarrow 00:28:22.812$  pluses what we really need because

NOTE Confidence: 0.86010612

 $00:28:22.812 \rightarrow 00:28:24.885$  the zeros have minimized, not,

NOTE Confidence: 0.86010612

 $00:28:24.885 \rightarrow 00:28:26.925$  I don't want to say they've gone away.

NOTE Confidence: 0.86010612

00:28:26.930 --> 00:28:28.094 If you ask pathologists,

NOTE Confidence: 0.86010612

00:28:28.094 --> 00:28:29.840 they will sternly tell you yes,

NOTE Confidence: 0.86010612

 $00{:}28{:}29{.}840 \dashrightarrow 00{:}28{:}32{.}066$  of course we still call IHC 0.

NOTE Confidence: 0.86010612

 $00{:}28{:}32.070 \dashrightarrow 00{:}28{:}33.610$  But.

NOTE Confidence: 0.86010612

 $00{:}28{:}33{.}610 \dashrightarrow 00{:}28{:}35{.}773$ Data will set will will tell us

NOTE Confidence: 0.86010612

 $00:28:35.773 \longrightarrow 00:28:38.493$  in a year or so from now how

 $00:28:38.493 \longrightarrow 00:28:39.865$  our IC0 calls changed.

NOTE Confidence: 0.86010612

 $00{:}28{:}39{.}870 \dashrightarrow 00{:}28{:}41{.}949$  But but I see one is now more common

NOTE Confidence: 0.86010612

 $00{:}28{:}41{.}949 \dashrightarrow 00{:}28{:}44{.}138$  and so if it's if it's more common

NOTE Confidence: 0.86010612

 $00:28:44.138 \rightarrow 00:28:46.149$  maybe that's the one we should be

NOTE Confidence: 0.86010612

 $00:28:46.149 \rightarrow 00:28:48.202$  measuring and in fact that's the plan.

NOTE Confidence: 0.86010612

 $00{:}28{:}48{.}202 \dashrightarrow 00{:}28{:}50{.}666$  So there are a few different ways

NOTE Confidence: 0.86010612

00:28:50.666 --> 00:28:53.097 we're going to study IHC equals one.

NOTE Confidence: 0.86010612

00:28:53.100 -> 00:28:56.040 The first is the Qdap Labs

NOTE Confidence: 0.86010612

 $00{:}28{:}56{.}040 \dashrightarrow 00{:}28{:}58{.}280$  prospective study and this is

NOTE Confidence: 0.86010612

 $00:28:58.280 \rightarrow 00:29:00.616$  copied with me by name by Nate Chan,

NOTE Confidence: 0.86010612

 $00{:}29{:}00{.}620 \dashrightarrow 00{:}29{:}02{.}540$  who's the director of the Q dot lab.

NOTE Confidence: 0.86010612

 $00:29:02.540 \longrightarrow 00:29:04.878$  And you can see we began August

NOTE Confidence: 0.86010612

 $00:29:04.878 \longrightarrow 00:29:07.312$  1 and we'll go till July 2023

NOTE Confidence: 0.86010612

 $00:29:07.312 \longrightarrow 00:29:09.325$  and today we have 226.

NOTE Confidence: 0.86010612

 $00:29:09.325 \rightarrow 00:29:11.515$  I anticipate we'll get around 400.

NOTE Confidence: 0.86010612

00:29:11.520 - 00:29:13.386 The inclusion criteria will be any

- NOTE Confidence: 0.86010612
- $00:29:13.386 \rightarrow 00:29:15.293$  case and the primary objective will
- NOTE Confidence: 0.86010612
- $00{:}29{:}15{.}293 \dashrightarrow 00{:}29{:}17{.}693$  be to determine the number of H0 cases
- NOTE Confidence: 0.86010612
- $00{:}29{:}17.753 \dashrightarrow 00{:}29{:}20.015$  that have detectable her two expression.
- NOTE Confidence: 0.86010612
- 00:29:20.020 --> 00:29:21.480 So how many IHC zeros?
- NOTE Confidence: 0.86010612
- $00{:}29{:}21{.}480 \dashrightarrow 00{:}29{:}22{.}815$  And this study was designed
- NOTE Confidence: 0.86010612
- $00:29:22.815 \rightarrow 00:29:23.349$  before everything.
- NOTE Confidence: 0.86010612
- 00:29:23.350 --> 00:29:24.205 Name HC One,
- NOTE Confidence: 0.86010612
- $00{:}29{:}24.205 \dashrightarrow 00{:}29{:}26.200$  but how many HC Zeros have above
- NOTE Confidence: 0.86010612
- $00{:}29{:}26{.}267 \dashrightarrow 00{:}29{:}28{.}395$  the limit of detection and how many
- NOTE Confidence: 0.86010612
- $00:29:28.395 \longrightarrow 00:29:30.819$  HC ones have below the limit of
- NOTE Confidence: 0.86010612
- $00{:}29{:}30{.}819 \dashrightarrow 00{:}29{:}32{.}985$  detection will be interesting as well.
- NOTE Confidence: 0.86010612
- $00{:}29{:}32{.}990 \dashrightarrow 00{:}29{:}34{.}109$  That's a secondary,
- NOTE Confidence: 0.86010612
- $00{:}29{:}34{.}109 \dashrightarrow 00{:}29{:}36{.}347$  that's a secondary objective of the
- NOTE Confidence: 0.86010612
- $00{:}29{:}36{.}347 \dashrightarrow 00{:}29{:}38{.}362$  study and the study is in process
- NOTE Confidence: 0.86010612
- $00:29:38.362 \rightarrow 00:29:40.637$  and we all just to show you a peak,
- NOTE Confidence: 0.86010612

 $00:29:40.640 \rightarrow 00:29:42.120$  we've already started doing some

NOTE Confidence: 0.86010612

00:29:42.120 --> 00:29:43.600 quantitative work and in fact

NOTE Confidence: 0.86010612

00:29:43.655 --> 00:29:45.090 you can see from quantitative,

NOTE Confidence: 0.86010612

 $00:29:45.090 \rightarrow 00:29:48.220$  this is quantification of prospective

NOTE Confidence: 0.86010612

 $00{:}29{:}48{.}220 \dashrightarrow 00{:}29{:}50{.}145$  tissue from the clinical trial

NOTE Confidence: 0.86010612

 $00{:}29{:}50{.}145 \dashrightarrow 00{:}29{:}53{.}009$  and you can see the lol in this

NOTE Confidence: 0.86010612

 $00{:}29{:}53{.}009 \dashrightarrow 00{:}29{:}55{.}240$  case was 33 and the OD is 3.

NOTE Confidence: 0.86010612

 $00{:}29{:}55{.}240 \dashrightarrow 00{:}29{:}57{.}000$  This is all done on the new platform

NOTE Confidence: 0.86010612

 $00{:}29{:}57{.}000 \dashrightarrow 00{:}29{:}58{.}820$  and you can see that there's a lot

NOTE Confidence: 0.86010612

 $00{:}29{:}58.820 \dashrightarrow 00{:}30{:}00{.}611$  of cases that are called zeros that

NOTE Confidence: 0.86010612

 $00{:}30{:}00{.}611 \dashrightarrow 00{:}30{:}02{.}315$  are above our limit of detection.

NOTE Confidence: 0.86010612

 $00:30:02.320 \longrightarrow 00:30:03.208$  There's not as many.

NOTE Confidence: 0.86010612

00:30:03.208 --> 00:30:04.811 So far it looks like we're going

NOTE Confidence: 0.86010612

00:30:04.811 --> 00:30:06.330 to not have very many that are

NOTE Confidence: 0.86010612

00:30:06.330 --> 00:30:07.720 below our limit of detection,

NOTE Confidence: 0.86010612

 $00:30:07.720 \longrightarrow 00:30:09.540$  but time will tell as we get

 $00:30:09.540 \longrightarrow 00:30:10.320$  as the study

NOTE Confidence: 0.833837779090909

 $00{:}30{:}10{.}391 \dashrightarrow 00{:}30{:}12{.}580$  matures. There's two other studies

NOTE Confidence: 0.833837779090909

 $00{:}30{:}12.580 \dashrightarrow 00{:}30{:}15.546$  that were progressing on one is a

NOTE Confidence: 0.833837779090909

 $00:30:15.546 \rightarrow 00:30:17.754$  TB CRC study report proposal with

NOTE Confidence: 0.833837779090909

00:30:17.754 --> 00:30:20.119 Ian and Eric's arrival at Yale,

NOTE Confidence: 0.833837779090909

 $00{:}30{:}20{.}120 \dashrightarrow 00{:}30{:}22{.}688$  we became part of the Translational

NOTE Confidence: 0.833837779090909

00:30:22.688 --> 00:30:24.400 Breast Cancer Research Consortium,

NOTE Confidence: 0.833837779090909

 $00:30:24.400 \longrightarrow 00:30:26.456$  which is a group of 16 or 17.

NOTE Confidence: 0.833837779090909

 $00{:}30{:}26{.}460 \dashrightarrow 00{:}30{:}28{.}590$  Now institutions that do studies

NOTE Confidence: 0.833837779090909

 $00:30:28.590 \longrightarrow 00:30:30.294$  together on translational research

NOTE Confidence: 0.833837779090909

 $00:30:30.294 \rightarrow 00:30:32.512$  and the goal of this study that

NOTE Confidence: 0.833837779090909

 $00:30:32.512 \longrightarrow 00:30:34.645$  is still in proposal stage is to

NOTE Confidence: 0.833837779090909

 $00{:}30{:}34.645 \dashrightarrow 00{:}30{:}36.175$  evaluate her two measurement in

NOTE Confidence: 0.833837779090909

 $00{:}30{:}36{.}175 \dashrightarrow 00{:}30{:}37{.}762$  the one plus metastatic cases.

NOTE Confidence: 0.833837779090909

 $00{:}30{:}37{.}762 \dashrightarrow 00{:}30{:}41{.}314$  So if we get one pluses and we get 2 or

00:30:41.314 --> 00:30:43.730 300 from 17 institutions around the country,

NOTE Confidence: 0.833837779090909

 $00:30:43.730 \longrightarrow 00:30:46.334$  we should be able to tell how

NOTE Confidence: 0.833837779090909

 $00:30:46.334 \rightarrow 00:30:48.120$  frequently we see the patients

NOTE Confidence: 0.833837779090909

 $00:30:48.120 \longrightarrow 00:30:50.130$  that have one plus actually don't

NOTE Confidence: 0.833837779090909

 $00:30:50.130 \longrightarrow 00:30:52.207$  have any target and vice versa,

NOTE Confidence: 0.833837779090909

 $00:30:52.210 \rightarrow 00:30:53.666$  we should be able to see response

NOTE Confidence: 0.833837779090909

 $00:30:53.666 \rightarrow 00:30:55.016$  since all those patients since they

NOTE Confidence: 0.833837779090909

 $00:30:55.016 \longrightarrow 00:30:56.591$  were called one plus will be get.

NOTE Confidence: 0.833837779090909

 $00:30:56.600 \rightarrow 00:30:58.217$  Drug will be getting trustors map drugs

NOTE Confidence: 0.833837779090909

 $00{:}30{:}58{.}217 \dashrightarrow 00{:}31{:}00{.}246$  he can and be present in the residency.

NOTE Confidence: 0.833837779090909

 $00{:}31{:}00{.}250 \dashrightarrow 00{:}31{:}02{.}610$  So here's the study a draft of the

NOTE Confidence: 0.833837779090909

 $00:31:02.610 \longrightarrow 00:31:04.441$  study objectives to evaluate the

NOTE Confidence: 0.833837779090909

 $00:31:04.441 \longrightarrow 00:31:06.013$  real world relationship between

NOTE Confidence: 0.833837779090909

 $00:31:06.013 \rightarrow 00:31:07.977$  quantitative her two expression QIF

NOTE Confidence: 0.833837779090909

 $00:31:07.977 \longrightarrow 00:31:09.772$  and objective response in patients

NOTE Confidence: 0.833837779090909

 $00:31:09.772 \longrightarrow 00:31:12.522$  with her two IHC plus one and

 $00:31:12.522 \rightarrow 00:31:14.612$  metastatic breast cancer receiving TXT.

NOTE Confidence: 0.833837779090909

 $00:31:14.620 \longrightarrow 00:31:17.077$  And then there's a number of secondary

NOTE Confidence: 0.833837779090909

 $00{:}31{:}17.077 \dashrightarrow 00{:}31{:}19.338$  objectives that are shown here as well.

NOTE Confidence: 0.833837779090909

 $00:31:19.340 \longrightarrow 00:31:21.174$  And then a second study that I,

NOTE Confidence: 0.833837779090909

 $00:31:21.180 \longrightarrow 00:31:23.524$  I don't even have a slide for yet

NOTE Confidence: 0.833837779090909

 $00:31:23.524 \rightarrow 00:31:26.388$  is that we proposed a study led by

NOTE Confidence: 0.833837779090909

00:31:26.388 --> 00:31:28.508 Merriam Lustberg here of patients

NOTE Confidence: 0.833837779090909

 $00:31:28.508 \rightarrow 00:31:31.396$  who get HC0 and then prospectively

NOTE Confidence: 0.833837779090909

 $00{:}31{:}31{.}396 \dashrightarrow 00{:}31{:}34{.}982$  giving them TXD much the way the

NOTE Confidence: 0.833837779090909

 $00:31:34.982 \rightarrow 00:31:37.592$  Daisy trial worked on that study

NOTE Confidence: 0.833837779090909

00:31:37.592 --> 00:31:39.808 is not yet completely designed

NOTE Confidence: 0.833837779090909

 $00:31:39.808 \rightarrow 00:31:42.078$  and not yet completely approved.

NOTE Confidence: 0.833837779090909

 $00{:}31{:}42.080 \dashrightarrow 00{:}31{:}43.655$  So I don't have any slides to discuss it,

NOTE Confidence: 0.833837779090909

00:31:43.660 --> 00:31:46.009 but I think those are the kinds of studies

NOTE Confidence: 0.833837779090909

 $00{:}31{:}46.009 \dashrightarrow 00{:}31{:}48.430$  we need where we have patient response.

 $00:31:48.430 \rightarrow 00:31:50.230$  Either real-world patient response or

NOTE Confidence: 0.833837779090909

 $00:31:50.230 \rightarrow 00:31:52.375$  clinical trial patient response in order

NOTE Confidence: 0.833837779090909

 $00:31:52.375 \rightarrow 00:31:54.440$  to figure out the animals per square

NOTE Confidence: 0.833837779090909

 $00:31:54.440 \rightarrow 00:31:56.229$  millimeter above which patients benefit.

NOTE Confidence: 0.833837779090909

 $00:31:56.230 \longrightarrow 00:31:57.490$  Will it be a cut point?

NOTE Confidence: 0.833837779090909

 $00:31:57.490 \longrightarrow 00:31:58.100$  Probably not.

NOTE Confidence: 0.833837779090909

 $00:31:58.100 \longrightarrow 00:31:59.930$  Probably there will be patients with

NOTE Confidence: 0.833837779090909

 $00:31:59.930 \rightarrow 00:32:01.528$  high animals per square millimeter

NOTE Confidence: 0.833837779090909

 $00:32:01.528 \longrightarrow 00:32:03.388$  that still don't benefit because there

NOTE Confidence: 0.833837779090909

 $00{:}32{:}03{.}388 \dashrightarrow 00{:}32{:}05{.}259$  are other mechanisms of resistance.

NOTE Confidence: 0.833837779090909

 $00{:}32{:}05{.}260 \dashrightarrow 00{:}32{:}07{.}268$  And I have and one of the interesting

NOTE Confidence: 0.833837779090909

 $00:32:07.268 \rightarrow 00:32:08.853$  topics that many labs are working

NOTE Confidence: 0.833837779090909

 $00:32:08.853 \rightarrow 00:32:10.752$  on including my own are what are

NOTE Confidence: 0.833837779090909

 $00:32:10.752 \longrightarrow 00:32:12.267$  the mechanisms of resistance beyond

NOTE Confidence: 0.833837779090909

 $00:32:12.267 \rightarrow 00:32:14.024$  just not enough her to present.

NOTE Confidence: 0.833837779090909

 $00:32:14.024 \rightarrow 00:32:15.928$  And hopefully next year or a couple

 $00:32:15.928 \dashrightarrow 00:32:18.146$  years from now I'll come back to you at

NOTE Confidence: 0.833837779090909

 $00:32:18.146 \rightarrow 00:32:19.868$  grand Rounds and talk about mechanisms

NOTE Confidence: 0.833837779090909

 $00:32:19.868 \rightarrow 00:32:22.082$  of resistance and a more complex assay

NOTE Confidence: 0.833837779090909

 $00:32:22.082 \rightarrow 00:32:25.036$  that also doesn't just assay her too,

NOTE Confidence: 0.833837779090909

 $00:32:25.040 \rightarrow 00:32:26.900$  but maybe assays other biomarkers

NOTE Confidence: 0.833837779090909

 $00:32:26.900 \dashrightarrow 00:32:28.760$  that are associated with resistance.

NOTE Confidence: 0.833837779090909

 $00:32:28.760 \longrightarrow 00:32:29.546$  Or other drugs.

NOTE Confidence: 0.833837779090909

 $00:32:29.546 \longrightarrow 00:32:31.380$  And in fact the her two trope

NOTE Confidence: 0.833837779090909

 $00:32:31.441 \longrightarrow 00:32:33.184$  2 assay as well along its way.

NOTE Confidence: 0.833837779090909

 $00:32:33.190 \dashrightarrow 00:32:35.542$  So we can help clinicians decide

NOTE Confidence: 0.833837779090909

00:32:35.542 --> 00:32:37.110 between Saskatoon Vova Tican,

NOTE Confidence: 0.833837779090909

 $00:32:37.110 \longrightarrow 00:32:40.652$  which is a trope 2 targeting therapy

NOTE Confidence: 0.833837779090909

00:32:40.652 --> 00:32:42.580 versus trastuzumab Drexel can.

NOTE Confidence: 0.833837779090909

 $00:32:42.580 \longrightarrow 00:32:44.638$  So for that my my last slide,

NOTE Confidence: 0.833837779090909

00:32:44.640 --> 00:32:47.160 overall HSR 2 assay is an LDT,

 $00:32:47.160 \rightarrow 00:32:49.640$  a lab developed test and not FDA approved.

NOTE Confidence: 0.833837779090909

00:32:49.640 --> 00:32:51.920 So if you only do FDA approved tests,

NOTE Confidence: 0.833837779090909

 $00:32:51.920 \longrightarrow 00:32:53.468$  you probably don't do them here

NOTE Confidence: 0.833837779090909

 $00:32:53.468 \rightarrow 00:32:55.416$  since most of our assays are LDT's,

NOTE Confidence: 0.833837779090909

 $00{:}32{:}55{.}416 \dashrightarrow 00{:}32{:}58{.}440$  but we do have a few FDA approved as says

NOTE Confidence: 0.811140847333333

 $00:32:58.521 \dashrightarrow 00:33:00.596$  and many FDA approved assays.

NOTE Confidence: 0.811140847333333

00:33:00.600 --> 00:33:01.564 People don't realize this,

NOTE Confidence: 0.811140847333333

00:33:01.564 --> 00:33:02.769 but being on the CAP

NOTE Confidence: 0.811140847333333

 $00:33:02.769 \longrightarrow 00:33:03.758$  committees you realize this,

NOTE Confidence: 0.811140847333333

 $00:33:03.760 \rightarrow 00:33:05.769$  if you change one step of the

NOTE Confidence: 0.811140847333333

 $00{:}33{:}05{.}769 \dashrightarrow 00{:}33{:}07{.}879$  protocol of your FDA approved as say,

NOTE Confidence: 0.811140847333333

 $00{:}33{:}07{.}880 \dashrightarrow 00{:}33{:}10{.}634$  it is then an LDT and you must thus

NOTE Confidence: 0.811140847333333

 $00{:}33{:}10.634 \dashrightarrow 00{:}33{:}12.540$  validate it and so most as says.

NOTE Confidence: 0.811140847333333

 $00:33:12.540 \longrightarrow 00:33:14.670$  We do are not FDA approved.

NOTE Confidence: 0.811140847333333

 $00:33:14.670 \rightarrow 00:33:16.710$  We might use FDA approved reagents,

NOTE Confidence: 0.811140847333333

 $00:33:16.710 \rightarrow 00:33:19.480$  but most assays we do are actually LDT's in

 $00:33:19.480 \dashrightarrow 00:33:21.970$  our lab and in all the labs around the world.

NOTE Confidence: 0.811140847333333

 $00:33:21.970 \longrightarrow 00:33:25.646$  And that also applies for molecular assays,

NOTE Confidence: 0.811140847333333

 $00:33:25.646 \longrightarrow 00:33:27.350$  gene mutation assays.

NOTE Confidence: 0.811140847333333

 $00:33:27.350 \longrightarrow 00:33:29.394$  Many of those assays are also not

NOTE Confidence: 0.811140847333333

 $00:33:29.394 \rightarrow 00:33:32.280$  FDA approved assays but rather LDT's.

NOTE Confidence: 0.811140847333333

 $00:33:32.280 \rightarrow 00:33:34.827$  HSR 2 essay is in the correct dynamic range.

NOTE Confidence: 0.811140847333333

 $00:33:34.830 \rightarrow 00:33:37.126$  That is, we're not weighing elephants on or

NOTE Confidence: 0.811140847333333

 $00:33:37.126 \rightarrow 00:33:39.316$  weighing mice on a scale built for elephants.

NOTE Confidence: 0.811140847333333

 $00:33:39.320 \dashrightarrow 00:33:41.175$  The level of target required for trustees,

NOTE Confidence: 0.811140847333333

 $00:33:41.180 \longrightarrow 00:33:42.846$  mab drugs decan is still unknown and

NOTE Confidence: 0.811140847333333

00:33:42.846 --> 00:33:44.630 I speak here before you and I don't

NOTE Confidence: 0.811140847333333

 $00:33:44.630 \rightarrow 00:33:46.378$  want to try to hide that from you.

NOTE Confidence: 0.811140847333333

 $00:33:46.380 \longrightarrow 00:33:48.156$  I think it's very clear that we don't

NOTE Confidence: 0.811140847333333

 $00{:}33{:}48.156 \dashrightarrow 00{:}33{:}49.999$  know the answer to this question yet.

NOTE Confidence: 0.811140847333333

 $00{:}33{:}50{.}000 \dashrightarrow 00{:}33{:}51{.}960$  But if we waited until we knew the answer to

 $00:33:52.009 \rightarrow 00:33:53.836$  the question before we started the essay,

NOTE Confidence: 0.811140847333333

 $00:33:53.840 \longrightarrow 00:33:56.162$  we would be years behind as as this essay.

NOTE Confidence: 0.811140847333333

00:33:56.170 - 00:33:57.886 We've been working on this essay

NOTE Confidence: 0.811140847333333

 $00:33:57.886 \longrightarrow 00:33:59.988$  for a couple years now to get it

NOTE Confidence: 0.811140847333333

 $00:33:59.988 \longrightarrow 00:34:01.332$  to the point that it's at.

NOTE Confidence: 0.811140847333333

 $00{:}34{:}01{.}340 \dashrightarrow 00{:}34{:}02{.}558$  And so now that we have.

NOTE Confidence: 0.811140847333333

 $00{:}34{:}02.560 \dashrightarrow 00{:}34{:}04.807$  Tools, I am asked that on cologists in

NOTE Confidence: 0.811140847333333

 $00:34:04.807 \rightarrow 00:34:06.839$  the audience ask for measurements,

NOTE Confidence: 0.811140847333333

 $00:34:06.840 \longrightarrow 00:34:07.944$  not for readings.

NOTE Confidence: 0.811140847333333

 $00:34:07.944 \rightarrow 00:34:10.152$  And please don't ask the pathologist

NOTE Confidence: 0.811140847333333

 $00:34:10.152 \longrightarrow 00:34:11.818$  to change their minds.

NOTE Confidence: 0.811140847333333

 $00:34:11.820 \longrightarrow 00:34:13.260$  That's persuasion Madison,

NOTE Confidence: 0.811140847333333

 $00{:}34{:}13.260 \dashrightarrow 00{:}34{:}14.700$  not precision medicine.

NOTE Confidence: 0.811140847333333

 $00:34:14.700 \rightarrow 00:34:16.446$  And we all respect our pathology

NOTE Confidence: 0.811140847333333

00:34:16.446 --> 00:34:18.039 colleagues and I think we all,

NOTE Confidence: 0.811140847333333

00:34:18.040 --> 00:34:18.632 you know,

 $00:34:18.632 \rightarrow 00:34:20.704$  I know that oncologists really think highly

NOTE Confidence: 0.811140847333333

 $00:34:20.704 \rightarrow 00:34:23.174$  of most of the pathologists they work with.

NOTE Confidence: 0.811140847333333

 $00:34:23.180 \dashrightarrow 00:34:25.294$  And I think that they don't realize

NOTE Confidence: 0.811140847333333

 $00:34:25.294 \rightarrow 00:34:27.503$  that when they do pursue persuasion

NOTE Confidence: 0.811140847333333

 $00{:}34{:}27{.}503 \dashrightarrow 00{:}34{:}29{.}445$  medicine that it's actually not

NOTE Confidence: 0.811140847333333

 $00:34:29.445 \longrightarrow 00:34:31.155$  what the biologist wants to hear.

NOTE Confidence: 0.811140847333333

 $00:34:31.160 \longrightarrow 00:34:33.274$  They don't want to be second guessed.

NOTE Confidence: 0.811140847333333

00:34:33.280 - 00:34:35.413 They want to if if if we're giving you

NOTE Confidence: 0.811140847333333

00:34:35.413 --> 00:34:37.400 a reading, we're giving you a reading,

NOTE Confidence: 0.811140847333333

 $00:34:37.400 \longrightarrow 00:34:38.920$  we really believe that's right.

NOTE Confidence: 0.811140847333333

 $00:34:38.920 \dashrightarrow 00:34:40.425$  And just like you shouldn't go back

NOTE Confidence: 0.811140847333333

00:34:40.425 -> 00:34:42.180 on the test and change your answer,

NOTE Confidence: 0.811140847333333

00:34:42.180 --> 00:34:43.972 don't change your answer.

NOTE Confidence: 0.811140847333333

 $00{:}34{:}43{.}972 \dashrightarrow 00{:}34{:}44{.}868$  It's if.

NOTE Confidence: 0.811140847333333

 $00{:}34{:}44{.}870 \dashrightarrow 00{:}34{:}46{.}190$  If that was your first impression,

 $00:34:46.190 \rightarrow 00:34:48.270$  it's probably your true impression

NOTE Confidence: 0.811140847333333

00:34:48.270 --> 00:34:50.350 and probably your best reading.

NOTE Confidence: 0.811140847333333

 $00:34:50.350 \longrightarrow 00:34:50.950$  And so with that,

NOTE Confidence: 0.811140847333333

 $00:34:50.950 \longrightarrow 00:34:52.051$  I just want to thank the people

NOTE Confidence: 0.811140847333333

 $00{:}34{:}52.051 \dashrightarrow 00{:}34{:}53.150$  in lab that do all the work.

NOTE Confidence: 0.811140847333333

00:34:53.150 --> 00:34:54.290 I get to talk about it,

NOTE Confidence: 0.811140847333333

 $00{:}34{:}54{.}290 \dashrightarrow 00{:}34{:}56{.}171$  but it's really a crew of people that do

NOTE Confidence: 0.811140847333333

 $00:34:56.171 \rightarrow 00:34:58.004$  all this stuff that I told you about.

NOTE Confidence: 0.811140847333333

 $00{:}34{:}58.010 \dashrightarrow 00{:}35{:}00.103$  I especially like to point out mirror

NOTE Confidence: 0.811140847333333

 $00{:}35{:}00{.}103 \dashrightarrow 00{:}35{:}02{.}357$  to Matafi who started that and started

NOTE Confidence: 0.811140847333333

 $00{:}35{:}02{.}357 \dashrightarrow 00{:}35{:}04{.}667$  building this essay in the lab over

NOTE Confidence: 0.811140847333333

 $00{:}35{:}04.667 \dashrightarrow 00{:}35{:}07.155$  two years ago now and then my Yale

NOTE Confidence: 0.811140847333333

 $00:35:07.155 \dashrightarrow 00:35:09.054$  collaborators and funding sources etcetera.

NOTE Confidence: 0.811140847333333

 $00:35:09.054 \rightarrow 00:35:11.862$  And then here's the the key

NOTE Confidence: 0.811140847333333

00:35:11.862 --> 00:35:14.004 group at our last holiday party,

NOTE Confidence: 0.811140847333333

00:35:14.010 -> 00:35:15.970 our lab group Aileen has now left.

- NOTE Confidence: 0.811140847333333
- $00{:}35{:}15{.}970 \dashrightarrow 00{:}35{:}17{.}506$  She was involved in a lot
- NOTE Confidence: 0.811140847333333
- $00:35:17.506 \longrightarrow 00:35:18.530$  of the analytic stuff.
- NOTE Confidence: 0.811140847333333
- $00:35:18.530 \dashrightarrow 00:35:20.474$  Matt Lou helped out with some of the.
- NOTE Confidence: 0.811140847333333
- $00{:}35{:}20{.}480 \dashrightarrow 00{:}35{:}21{.}988$  Analytic stuff as well.
- NOTE Confidence: 0.811140847333333
- $00{:}35{:}21{.}988 \dashrightarrow 00{:}35{:}24{.}108$  And then and Jack and Katie
- NOTE Confidence: 0.811140847333333
- $00:35:24.108 \longrightarrow 00:35:25.020$  weren't at the party,
- NOTE Confidence: 0.811140847333333
- $00:35:25.020 \rightarrow 00:35:26.820$  so they got their picture separate.
- NOTE Confidence: 0.797865172727273
- $00:35:26.820 \longrightarrow 00:35:28.344$  So with now, I've also left
- NOTE Confidence: 0.797865172727273
- 00:35:28.344 --> 00:35:29.950 about 20 minutes for questions,
- NOTE Confidence: 0.797865172727273
- $00:35:29.950 \longrightarrow 00:35:30.750$  if there are questions.
- NOTE Confidence: 0.797865172727273
- 00:35:30.750 --> 00:35:31.550 Thank you very much.
- NOTE Confidence: 0.86163855125
- $00{:}35{:}40{.}150 \dashrightarrow 00{:}35{:}42{.}830$  So we have 4 questions in the chat.
- NOTE Confidence: 0.86163855125
- 00:35:42.830 --> 00:35:44.130 Maybe while you're warming up,
- NOTE Confidence: 0.86163855125
- $00{:}35{:}44{.}130 \dashrightarrow 00{:}35{:}45{.}270$  should I start with those?
- NOTE Confidence: 0.86163855125
- $00{:}35{:}45{.}270 \dashrightarrow 00{:}35{:}46{.}450$  Oh no, there's only two.
- NOTE Confidence: 0.86163855125

 $00:35:46.450 \dashrightarrow 00:35:47.958$  What about discordance with

NOTE Confidence: 0.86163855125

 $00{:}35{:}47{.}958 \dashrightarrow 00{:}35{:}49{.}466$  pathologists reading the same

NOTE Confidence: 0.86163855125

00:35:49.466 --> 00:35:51.189 slides after a washout period?

NOTE Confidence: 0.86163855125

00:35:51.190 --> 00:35:52.501 So Manju Prasad,

NOTE Confidence: 0.86163855125

00:35:52.501 --> 00:35:55.123 a esteemed pathologist in our department,

NOTE Confidence: 0.86163855125

 $00:35:55.130 \rightarrow 00:35:57.792$  asks a very pivotal question, that is.

NOTE Confidence: 0.86163855125

 $00:35:57.792 \longrightarrow 00:35:59.647$  When you're doing any kind

NOTE Confidence: 0.86163855125

00:35:59.647 --> 00:36:00.760 of pathologist study,

NOTE Confidence: 0.86163855125

 $00{:}36{:}00{.}760 \dashrightarrow 00{:}36{:}01{.}830$  when you read it once,

NOTE Confidence: 0.86163855125

 $00:36:01.830 \longrightarrow 00:36:02.817$  if you're going to read it again,

NOTE Confidence: 0.86163855125

 $00{:}36{:}02.820 \dashrightarrow 00{:}36{:}04.200$  you should have a washout period.

NOTE Confidence: 0.86163855125

 $00:36:04.200 \longrightarrow 00:36:05.928$  That is so you don't remember

NOTE Confidence: 0.86163855125

 $00:36:05.928 \dashrightarrow 00:36:07.080$  that case because surprisingly,

NOTE Confidence: 0.86163855125

 $00:36:07.080 \rightarrow 00:36:09.110$  pathologists have a really good memory for

NOTE Confidence: 0.86163855125

 $00:36:09.110 \longrightarrow 00:36:10.918$  what the morphology of cases look like,

NOTE Confidence: 0.86163855125

 $00:36:10.920 \longrightarrow 00:36:12.714$  and they can also remember the
- NOTE Confidence: 0.86163855125
- $00:36:12.714 \longrightarrow 00:36:14.320$  patient's name on the label.
- NOTE Confidence: 0.86163855125
- $00{:}36{:}14{.}320 \dashrightarrow 00{:}36{:}16{.}322$  And so a lot of studies have
- NOTE Confidence: 0.86163855125
- $00:36:16.322 \longrightarrow 00:36:17.180$  a washout period.
- NOTE Confidence: 0.86163855125
- $00{:}36{:}17.180 \dashrightarrow 00{:}36{:}19.196$  We didn't need a washout period in this
- NOTE Confidence: 0.86163855125
- $00:36:19.196 \rightarrow 00:36:21.179$  study because they only saw the slides once.
- NOTE Confidence: 0.86163855125
- $00{:}36{:}21.180 \dashrightarrow 00{:}36{:}23.241$  So if we're going to show them to them
- NOTE Confidence: 0.86163855125
- $00:36:23.241 \rightarrow 00:36:25.063$  again and if we're going to do any
- NOTE Confidence: 0.86163855125
- $00:36:25.063 \rightarrow 00:36:27.079$  kind of intra observer reproducibility,
- NOTE Confidence: 0.86163855125
- $00{:}36{:}27.080 \dashrightarrow 00{:}36{:}28.532$  which we didn't do and some
- NOTE Confidence: 0.86163855125
- $00:36:28.532 \rightarrow 00:36:29.500$  other studies have done,
- NOTE Confidence: 0.86163855125
- $00:36:29.500 \rightarrow 00:36:30.718$  we would need a washout period.
- NOTE Confidence: 0.86163855125
- 00:36:30.720 --> 00:36:31.960 But in this case,
- NOTE Confidence: 0.86163855125
- $00:36:31.960 \rightarrow 00:36:33.820$  a washout period was not required.
- NOTE Confidence: 0.86163855125
- $00{:}36{:}33{.}820 \dashrightarrow 00{:}36{:}36{.}620$  And then Timothy Robinson asks,
- NOTE Confidence: 0.86163855125
- $00:36:36.620 \longrightarrow 00:36:37.715$  is heterogeneity within
- NOTE Confidence: 0.86163855125

 $00:36:37.715 \longrightarrow 00:36:39.175$  the tumor important issue?

NOTE Confidence: 0.86163855125

 $00{:}36{:}39{.}180 \dashrightarrow 00{:}36{:}40{.}716$  Is it more important to do a small

NOTE Confidence: 0.86163855125

 $00{:}36{:}40.716 \dashrightarrow 00{:}36{:}41.791$  percentage of cancer cells that

NOTE Confidence: 0.86163855125

 $00:36:41.791 \rightarrow 00:36:43.291$  express a high amount of heart, too?

NOTE Confidence: 0.86163855125

 $00{:}36{:}43.291 \dashrightarrow 00{:}36{:}44.819$  Or is it more important to know that

NOTE Confidence: 0.86163855125

 $00{:}36{:}44{.}819 \dashrightarrow 00{:}36{:}46{.}609$  a high number of cells expressed at

NOTE Confidence: 0.86163855125

 $00:36:46.609 \rightarrow 00:36:48.179$  least the minimum amount of her too?

NOTE Confidence: 0.86163855125

 $00:36:48.180 \longrightarrow 00:36:49.530$  Wow, phenomenal question.

NOTE Confidence: 0.86163855125

 $00{:}36{:}49{.}530 \dashrightarrow 00{:}36{:}51{.}476$  That's Jax three, that's his.

NOTE Confidence: 0.86163855125

00:36:51.476 --> 00:36:52.072 Thesis project,

NOTE Confidence: 0.86163855125

 $00{:}36{:}52{.}072 \dashrightarrow 00{:}36{:}53{.}860$  I think that's a great question.

NOTE Confidence: 0.86163855125

 $00{:}36{:}53.860 \dashrightarrow 00{:}36{:}55.636$  We obviously don't know the answer.

NOTE Confidence: 0.86163855125

 $00:36:55.640 \rightarrow 00:36:57.200$  All the pathologists in the audience

NOTE Confidence: 0.86163855125

 $00:36:57.200 \rightarrow 00:36:59.359$  know that her two is very heterogeneous.

NOTE Confidence: 0.86163855125

 $00:36:59.360 \longrightarrow 00:37:01.245$  Not only is it heterogeneous

NOTE Confidence: 0.86163855125

 $00:37:01.245 \longrightarrow 00:37:02.753$  from within a slide,

 $00:37:02.760 \longrightarrow 00:37:04.720$  but it's heterogeneous between cuts.

NOTE Confidence: 0.86163855125

 $00{:}37{:}04.720 \dashrightarrow 00{:}37{:}06.400$  And all the pathologists in the audience

NOTE Confidence: 0.86163855125

 $00{:}37{:}06{.}400 \dashrightarrow 00{:}37{:}08{.}037$  know that when we sample one core

NOTE Confidence: 0.86163855125

 $00:37:08.037 \longrightarrow 00:37:09.841$  biopsy that's less than 1% of the tumor.

NOTE Confidence: 0.86163855125

 $00{:}37{:}09{.}841 \dashrightarrow 00{:}37{:}12{.}282$  And so there's no way for us to actually

NOTE Confidence: 0.86163855125

 $00{:}37{:}12.282 \dashrightarrow 00{:}37{:}14.087$  answer that question about true

NOTE Confidence: 0.86163855125

 $00:37:14.087 \rightarrow 00:37:16.080$  heterogeneity of the patients tumor.

NOTE Confidence: 0.86163855125

 $00:37:16.080 \longrightarrow 00:37:16.980$  But what we can add,

NOTE Confidence: 0.86163855125

 $00{:}37{:}16{.}980 \dashrightarrow 00{:}37{:}18{.}345$  we can ask about heterogeneity

NOTE Confidence: 0.86163855125

 $00:37:18.345 \longrightarrow 00:37:20.613$  on the slide and we can and are

NOTE Confidence: 0.86163855125

 $00:37:20.613 \rightarrow 00:37:21.737$  asking at that question.

NOTE Confidence: 0.86163855125

 $00{:}37{:}21.740 \dashrightarrow 00{:}37{:}22.344$  That is,

NOTE Confidence: 0.86163855125

 $00:37:22.344 \rightarrow 00:37:23.854$  how important is high expression

NOTE Confidence: 0.86163855125

 $00:37:23.854 \longrightarrow 00:37:25.855$  in a single cell versus high

NOTE Confidence: 0.86163855125

 $00:37:25.855 \rightarrow 00:37:27.570$  expression in the average cell?

NOTE Confidence: 0.86163855125

 $00:37:27.570 \longrightarrow 00:37:28.610$  We started with the average.

NOTE Confidence: 0.86163855125

 $00{:}37{:}28.610 \dashrightarrow 00{:}37{:}30.110$  You have to start somewhere,

NOTE Confidence: 0.86163855125

 $00{:}37{:}30{.}110 \dashrightarrow 00{:}37{:}31{.}454$  and I don't know that the

NOTE Confidence: 0.86163855125

 $00:37:31.454 \rightarrow 00:37:32.750$  average is a correct answer.

NOTE Confidence: 0.86163855125

00:37:32.750 --> 00:37:34.325 You could argue because of

NOTE Confidence: 0.86163855125

 $00{:}37{:}34{.}325 \dashrightarrow 00{:}37{:}35{.}943$  the by stander effect of TDXD,

NOTE Confidence: 0.86163855125

 $00:37:35.943 \longrightarrow 00:37:37.708$  it's actually the highest ones

NOTE Confidence: 0.86163855125

00:37:37.708 - > 00:37:39.890 that make the most difference,

NOTE Confidence: 0.86163855125

 $00:37:39.890 \longrightarrow 00:37:41.370$  but we don't know that.

NOTE Confidence: 0.86163855125

 $00:37:41.370 \longrightarrow 00:37:44.670$  That's just speculation at this point.

NOTE Confidence: 0.86163855125

00:37:44.670 --> 00:37:49.398 Let's see. Now it's your turn.

NOTE Confidence: 0.86163855125

 $00:37:49.400 \longrightarrow 00:37:50.810$  It doesn't.

NOTE Confidence: 0.86163855125

 $00{:}37{:}50{.}810 \dashrightarrow 00{:}37{:}51{.}240$  Say.

NOTE Confidence: 0.87842585

 $00:37:54.980 \longrightarrow 00:37:56.140$  That's a great question.

NOTE Confidence: 0.798758137692308

 $00{:}37{:}59{.}010 \dashrightarrow 00{:}37{:}59{.}882$  We can do more.

NOTE Confidence: 0.798758137692308

 $00:37:59.882 \rightarrow 00:38:02.249$  So as soon as I had the assay built,

00:38:02.250 --> 00:38:04.902 I applied for tissue from AstraZeneca

NOTE Confidence: 0.798758137692308

 $00{:}38{:}04{.}902 \dashrightarrow 00{:}38{:}07{.}867$ adicci senko from the Destiny 4 trial

NOTE Confidence: 0.798758137692308

 $00:38:07.867 \longrightarrow 00:38:11.240$  and was rapidly told I would never see that.

NOTE Confidence: 0.798758137692308

00:38:11.240 --> 00:38:14.200 And it's, I don't fault them for that.

NOTE Confidence: 0.798758137692308

 $00:38:14.200 \longrightarrow 00:38:16.414$  They have their own people that

NOTE Confidence: 0.798758137692308

 $00:38:16.414 \rightarrow 00:38:18.584$  can do quantitative work and they

NOTE Confidence: 0.798758137692308

00:38:18.584 --> 00:38:20.666 have an FDA approval for IHC 0123.

NOTE Confidence: 0.798758137692308

 $00:38:20.666 \longrightarrow 00:38:22.507$  So they don't want to have to

NOTE Confidence: 0.798758137692308

00:38:22.507 --> 00:38:23.918 change their FDA approval.

NOTE Confidence: 0.798758137692308

 $00:38:23.920 \rightarrow 00:38:25.712$  They're making a lot of money on this

NOTE Confidence: 0.798758137692308

 $00:38:25.712 \longrightarrow 00:38:27.647$  drug and it would be detrimental to

NOTE Confidence: 0.798758137692308

 $00{:}38{:}27.647 \dashrightarrow 00{:}38{:}29.368$  the shareholders of that company to

NOTE Confidence: 0.798758137692308

 $00{:}38{:}29{.}368 \dashrightarrow 00{:}38{:}30{.}985$  have me have access to that tissue.

NOTE Confidence: 0.9305174

 $00:38:33.870 \dashrightarrow 00:38:36.688$  My question was how much heterogeneity NOTE Confidence: 0.9305174

 $00:38:36.690 \dashrightarrow 00:38:39.000$  do you see in the ATOMAL expression?

NOTE Confidence: 0.9305174

00:38:39.000 --> 00:38:41.072 Because you're taking so many fields of

NOTE Confidence: 0.9305174

00:38:41.072 --> 00:38:43.441 view and taking an average, do you see

NOTE Confidence: 0.9305174

 $00:38:43.441 \rightarrow 00:38:46.430$  a lot of heterogeneity there or is it?

NOTE Confidence: 0.9305174

 $00:38:46.430 \longrightarrow 00:38:49.230$  So that's a great question.

NOTE Confidence: 0.9305174

 $00{:}38{:}49{.}230 \dashrightarrow 00{:}38{:}51{.}062$  Heterogeneity within a core

NOTE Confidence: 0.9305174

 $00{:}38{:}51{.}062 \dashrightarrow 00{:}38{:}52{.}894$  biopsy is quite substantial.

NOTE Confidence: 0.9305174

 $00{:}38{:}52{.}900 \dashrightarrow 00{:}38{:}54{.}756$  And as you know when you read them,

NOTE Confidence: 0.9305174

 $00:38:54.760 \rightarrow 00:38:57.316$  you see bright areas and not so bright areas.

NOTE Confidence: 0.9305174

 $00{:}38{:}57{.}320 \dashrightarrow 00{:}38{:}59{.}360$  And you know how do we handle that?

NOTE Confidence: 0.9305174

 $00:38:59.360 \dashrightarrow 00:39:01.220$  Well, someday we'll know how you

NOTE Confidence: 0.9305174

 $00{:}39{:}01{.}220 \dashrightarrow 00{:}39{:}03{.}423$  know whether it's the highest sell or

NOTE Confidence: 0.9305174

 $00{:}39{:}03{.}423 \dashrightarrow 00{:}39{:}05{.}516$  the average sell or the lowest sell.

NOTE Confidence: 0.9305174

 $00:39:05.520 \longrightarrow 00:39:07.200$  That's most important for response

NOTE Confidence: 0.9305174

 $00{:}39{:}07{.}200 \dashrightarrow 00{:}39{:}08{.}544$  to Trump drug seeking.

NOTE Confidence: 0.9305174

 $00:39:08.550 \longrightarrow 00:39:10.056$  But we don't know that yet.

NOTE Confidence: 0.9305174

 $00:39:10.060 \rightarrow 00:39:12.644$  And so in the same vein of OK,

- NOTE Confidence: 0.9305174
- $00:39:12.650 \rightarrow 00:39:14.855$  we're just going to take a core biopsy and
- NOTE Confidence: 0.9305174
- $00{:}39{:}14.855 \dashrightarrow 00{:}39{:}17.125$  say that that represents the whole tumor,
- NOTE Confidence: 0.9305174
- $00:39:17.130 \longrightarrow 00:39:18.324$  we're going to just take the
- NOTE Confidence: 0.9305174
- $00:39:18.324 \rightarrow 00:39:19.370$  average and say that that.
- NOTE Confidence: 0.9305174
- $00:39:19.370 \longrightarrow 00:39:22.136$  Represents the expression of her too.
- NOTE Confidence: 0.9305174
- $00:39:22.140 \longrightarrow 00:39:22.990$  And the second question
- NOTE Confidence: 0.9305174
- $00:39:22.990 \longrightarrow 00:39:24.615$  moved for the clinician.
- NOTE Confidence: 0.9305174
- $00:39:24.615 \rightarrow 00:39:27.430$  We see situations with heterogeneity
- NOTE Confidence: 0.9305174
- $00{:}39{:}27{.}430 \dashrightarrow 00{:}39{:}30{.}522$  where we have a clear 3 plus tumor where
- NOTE Confidence: 0.9305174
- $00:39:30.522 \rightarrow 00:39:32.928$  the patient gets you know trastuzumab
- NOTE Confidence: 0.9305174
- $00{:}39{:}32{.}928 \dashrightarrow 00{:}39{:}34{.}988$  and there's complete response and
- NOTE Confidence: 0.9305174
- 00:39:34.988 --> 00:39:37.358 there's another tumor which was her
- NOTE Confidence: 0.9305174
- 00:39:37.358 00:39:39.715 to negative and was zero or you
- NOTE Confidence: 0.9305174
- $00{:}39{:}39{.}715 \dashrightarrow 00{:}39{:}41{.}942$  know one plus which didn't respond.
- NOTE Confidence: 0.9305174
- $00{:}39{:}41{.}942 \dashrightarrow 00{:}39{:}44{.}828$  So what will these patients benefit
- NOTE Confidence: 0.9305174

- $00:39:44.828 \rightarrow 00:39:48.120$  from a second round of DXD or
- NOTE Confidence: 0.9305174
- $00:39:48.120 \longrightarrow 00:39:51.630$  when they have two distinct?

 $00{:}39{:}51{.}630 \dashrightarrow 00{:}39{:}54{.}780$  Her two profiles to maybe I can use the

NOTE Confidence: 0.9305174

 $00:39:54.780 \rightarrow 00:39:57.370$  microphone since there's 71 people online.

NOTE Confidence: 0.71368902

 $00:39:58.240 \longrightarrow 00:39:59.934$  Yeah, when I but I, I do want

NOTE Confidence: 0.71368902

 $00:39:59.934 \rightarrow 00:40:00.924$  to clarify the question because,

NOTE Confidence: 0.71368902

00:40:00.930 --> 00:40:02.530 I mean we wouldn't use.

NOTE Confidence: 0.837351195714286

 $00{:}40{:}04.690 \dashrightarrow 00{:}40{:}06.895$  We wouldn't have used a standard her

NOTE Confidence: 0.837351195714286

 $00{:}40{:}06.895 \dashrightarrow 00{:}40{:}09.077$  two the rapy if they were one plus.

NOTE Confidence: 0.6665299375

 $00:40:13.180 \longrightarrow 00:40:13.940$  Why don't we choose?

NOTE Confidence: 0.8049838

 $00{:}40{:}18.090 \dashrightarrow 00{:}40{:}22.410$  Do we use her two therapy, I mean. Yeah.

NOTE Confidence: 0.832513583333333

 $00:40:24.600 \longrightarrow 00:40:25.428$  But the patient?

NOTE Confidence: 0.5355477925

 $00{:}40{:}29{.}210 \dashrightarrow 00{:}40{:}30{.}598$  Patient had complete response

NOTE Confidence: 0.69599822

 $00:40:30.610 \rightarrow 00:40:33.874$  to that through. So it was our CB0,

NOTE Confidence: 0.69599822

 $00:40:33.880 \longrightarrow 00:40:36.364$  but then the tumor which was

NOTE Confidence: 0.69599822

 $00:40:36.364 \rightarrow 00:40:38.020$  one plus still extensive.

 $00:40:39.340 \longrightarrow 00:40:41.044$  Yeah so I mean it depends

NOTE Confidence: 0.881571676

 $00:40:41.044 \longrightarrow 00:40:42.180$  on the clinical situation.

NOTE Confidence: 0.881571676

 $00{:}40{:}42.180 \dashrightarrow 00{:}40{:}44.616$  We know pretty clearly now that with

NOTE Confidence: 0.881571676

 $00:40:44.620 \rightarrow 00:40:46.880$  before you know with the previous

NOTE Confidence: 0.881571676

00:40:46.880 --> 00:40:48.826 generation of her two the rapies that

NOTE Confidence: 0.881571676

 $00{:}40{:}48.826 \dashrightarrow 00{:}40{:}51.017$  you do not see any benefit with non

NOTE Confidence: 0.881571676

 $00:40:51.017 \rightarrow 00:40:53.519$  her 2/3 plus or amplified cancer.

NOTE Confidence: 0.881571676

 $00{:}40{:}53{.}520 \dashrightarrow 00{:}40{:}55{.}000$  So the her two lows do not respond

NOTE Confidence: 0.881571676

 $00{:}40{:}55{.}000 \dashrightarrow 00{:}40{:}56{.}801$  to the previous generation any of the

NOTE Confidence: 0.881571676

 $00{:}40{:}56.801 \dashrightarrow 00{:}40{:}58.680$  previous generation of her two the rapies.

NOTE Confidence: 0.881571676

 $00{:}40{:}58.680 \dashrightarrow 00{:}41{:}01.326$  So but with now with Tristan Madrox

NOTE Confidence: 0.881571676

00:41:01.326 --> 00:41:03.838 taken you know I think you could

NOTE Confidence: 0.881571676

00:41:03.838 --> 00:41:06.346 you know make a case that you know

NOTE Confidence: 0.881571676

 $00{:}41{:}06{.}346 \dashrightarrow 00{:}41{:}08{.}014$  you might you would see potentially

NOTE Confidence: 0.881571676

 $00{:}41{:}08.014 \dashrightarrow 00{:}41{:}09.299$  could see benefit both.

NOTE Confidence: 0.881571676

 $00:41:09.300 \longrightarrow 00:41:10.890$  And that clearly amplified in

NOTE Confidence: 0.881571676

 $00:41:10.890 \longrightarrow 00:41:12.162$  the her two lows.

NOTE Confidence: 0.881571676

00:41:12.170 --> 00:41:13.899 But prior to that we would look

NOTE Confidence: 0.881571676

00:41:13.899 --> 00:41:16.185 at a case like that on a case by

NOTE Confidence: 0.881571676

00:41:16.185 --> 00:41:18.049 case basis and say well let's use

NOTE Confidence: 0.881571676

 $00:41:18.049 \longrightarrow 00:41:20.262$  the her two therapy to get rid of NOTE Confidence: 0.881571676

 $00{:}41{:}20{.}262 \dashrightarrow 00{:}41{:}21{.}822$  that usually more aggressive her

NOTE Confidence: 0.881571676

 $00{:}41{:}21.822 \dashrightarrow 00{:}41{:}23.726$  two her two positive cancer and

NOTE Confidence: 0.881571676

 $00{:}41{:}23.726 \dashrightarrow 00{:}41{:}25.826$  then we'll worry about the her two NOTE Confidence: 0.881571676

 $00{:}41{:}25.826 \dashrightarrow 00{:}41{:}27.750$  negative or her two low cancer later.

NOTE Confidence: 0.881571676

 $00:41:27.750 \longrightarrow 00:41:29.556$  But it's it's you know again the

NOTE Confidence: 0.881571676

 $00:41:29.556 \rightarrow 00:41:31.625$  the field is evolving now that we

NOTE Confidence: 0.881571676

 $00{:}41{:}31.625 \dashrightarrow 00{:}41{:}33.479$  have these drugs that work across

NOTE Confidence: 0.881571676

 $00:41:33.544 \longrightarrow 00:41:35.149$  different levels of her too.

NOTE Confidence: 0.881571676

 $00{:}41{:}35{.}150 \dashrightarrow 00{:}41{:}36{.}958$  I mean getting to in your earlier point

NOTE Confidence: 0.881571676

 $00:41:36.958 \rightarrow 00:41:38.606$  that the two questions were brought

- NOTE Confidence: 0.881571676
- $00:41:38.606 \rightarrow 00:41:40.328$  up about her two heterogeneity and
- NOTE Confidence: 0.881571676
- 00:41:40.378 --> 00:41:41.978 I think that's really interesting.
- NOTE Confidence: 0.881571676
- $00:41:41.980 \longrightarrow 00:41:43.520$  Again with the first generation,
- NOTE Confidence: 0.881571676
- $00:41:43.520 \rightarrow 00:41:45.655$  her two therapies, it was very clear.
- NOTE Confidence: 0.881571676
- 00:41:45.660 --> 00:41:47.150 We actually did a prospective,
- NOTE Confidence: 0.881571676
- $00{:}41{:}47{.}150 \dashrightarrow 00{:}41{:}51{.}098$  big prospective trial with with the other,
- NOTE Confidence: 0.881571676
- 00:41:51.100 --> 00:41:53.390 the first antibody drug conjugate
- NOTE Confidence: 0.881571676
- $00{:}41{:}53{.}390 \dashrightarrow 00{:}41{:}55{.}680$  that doesn't have by stander effect
- NOTE Confidence: 0.881571676
- $00:41:55.748 \longrightarrow 00:41:58.172$  and in that study a heterogeneous
- NOTE Confidence: 0.881571676
- $00:41:58.172 \rightarrow 00:42:00.530$  cancer responded much work much less.
- NOTE Confidence: 0.881571676
- $00:42:00.530 \longrightarrow 00:42:02.315$  Effectively to a heterogeneous cancer
- NOTE Confidence: 0.881571676
- $00{:}42{:}02{.}315 \dashrightarrow 00{:}42{:}05{.}016$  than it did to a non heterogeneous
- NOTE Confidence: 0.881571676
- $00{:}42{:}05{.}016 \dashrightarrow 00{:}42{:}07{.}131$  cancer and and quantitatively that
- NOTE Confidence: 0.881571676
- $00{:}42{:}07{.}131 \dashrightarrow 00{:}42{:}09{.}621$  the to your specific question what
- NOTE Confidence: 0.881571676
- $00{:}42{:}09{.}621 \dashrightarrow 00{:}42{:}12{.}302$  mattered was the percent of her two
- NOTE Confidence: 0.881571676

 $00:42:12.310 \longrightarrow 00:42:14.575$  negative cells not the intensity

NOTE Confidence: 0.881571676

 $00{:}42{:}14.575 \dashrightarrow 00{:}42{:}18.120$  of her two on themselves.

NOTE Confidence: 0.881571676

 $00{:}42{:}18{.}120 \dashrightarrow 00{:}42{:}20{.}507$  Again with a drug that has by stander

NOTE Confidence: 0.881571676

 $00{:}42{:}20.507 \dashrightarrow 00{:}42{:}23.281$  effect as as I think David was alluding

NOTE Confidence: 0.881571676

 $00{:}42{:}23.281 \dashrightarrow 00{:}42{:}25.144$  to that might be switched and may be

NOTE Confidence: 0.881571676

 $00:42:25.144 \longrightarrow 00:42:27.237$  just if you just need to have a

NOTE Confidence: 0.881571676

00:42:27.237 --> 00:42:28.761 certain number of her two strongly

NOTE Confidence: 0.881571676

 $00:42:28.821 \rightarrow 00:42:30.585$  positive cells to get the drug in.

NOTE Confidence: 0.881571676

 $00{:}42{:}30{.}590 \dashrightarrow 00{:}42{:}32{.}182$  And then the and then the by stander effect

NOTE Confidence: 0.881571676

 $00{:}42{:}32{.}182 \dashrightarrow 00{:}42{:}33{.}970$  will take care of the her two negative cells.

NOTE Confidence: 0.881571676

00:42:33.970 --> 00:42:35.230 We like to test out

NOTE Confidence: 0.881571676

 $00:42:35.230 \longrightarrow 00:42:37.908$  prospectively with we haven't.

NOTE Confidence: 0.881571676

 $00:42:37.910 \longrightarrow 00:42:39.334$  Had the funding yet to do that trial.

NOTE Confidence: 0.68209848

00:42:41.730 --> 00:42:44.298 Yeah. And I enjoy your talk, David.

NOTE Confidence: 0.886226237142857

 $00:42:46.080 \longrightarrow 00:42:49.727$  Is any do you have any information?

NOTE Confidence: 0.886226237142857

 $00:42:49.730 \longrightarrow 00:42:53.588$  The conjugate drug can get activated.

- NOTE Confidence: 0.886226237142857
- $00:42:53.590 \longrightarrow 00:42:55.880$  In the extracellular and
- NOTE Confidence: 0.886226237142857
- $00{:}42{:}55{.}880 \dashrightarrow 00{:}42{:}57{.}774$  microenvironment of tumor cells.
- NOTE Confidence: 0.886226237142857
- $00{:}42{:}57{.}774 \dashrightarrow 00{:}43{:}01{.}110$  So I I would again defer to Ian,
- NOTE Confidence: 0.886226237142857
- $00{:}43{:}01{.}110 \dashrightarrow 00{:}43{:}01{.}940$  who's much more of an
- NOTE Confidence: 0.886226237142857
- $00{:}43{:}01{.}940 \dashrightarrow 00{:}43{:}02{.}930$  expert on this than I am.
- NOTE Confidence: 0.886226237142857
- $00{:}43{:}02{.}930 \dashrightarrow 00{:}43{:}05{.}324$  But it's my understanding that the drug,
- NOTE Confidence: 0.886226237142857
- $00:43:05.330 \longrightarrow 00:43:06.466$  once it comes off,
- NOTE Confidence: 0.886226237142857
- $00:43:06.466 \rightarrow 00:43:08.790$  it has to be cleaved inside the cell.
- NOTE Confidence: 0.886226237142857
- 00:43:08.790 --> 00:43:09.850 But once it comes off,
- NOTE Confidence: 0.886226237142857
- $00:43:09.850 \longrightarrow 00:43:12.550$  it survives in the extracellular environment.
- NOTE Confidence: 0.886226237142857
- $00:43:12.550 \rightarrow 00:43:14.419$  And that's how the bystander effect works.
- NOTE Confidence: 0.886226237142857
- $00:43:14.420 \longrightarrow 00:43:16.408$  That's how it can kill neighboring cells.
- NOTE Confidence: 0.886226237142857
- $00:43:16.410 \longrightarrow 00:43:20.100$  Bystander effect doesn't really require.
- NOTE Confidence: 0.886226237142857
- $00{:}43{:}20.100 \dashrightarrow 00{:}43{:}25.430$  To go into the cells as long as it's a.
- NOTE Confidence: 0.886226237142857
- $00{:}43{:}25{.}430 \dashrightarrow 00{:}43{:}28{.}320$  Present in the microenvironment of the
- NOTE Confidence: 0.886226237142857

 $00:43:28.320 \longrightarrow 00:43:30.750$  tumor cell in the enriched fashion

NOTE Confidence: 0.886226237142857

 $00{:}43{:}30{.}750 \dashrightarrow 00{:}43{:}32{.}649$  you you will have some activities.

NOTE Confidence: 0.886226237142857

 $00:43:32.649 \longrightarrow 00:43:34.767$  Well the drug is an inhibitor

NOTE Confidence: 0.886226237142857

 $00:43:34.767 \longrightarrow 00:43:36.110$  of topoisomerase,

NOTE Confidence: 0.886226237142857

 $00:43:36.110 \dashrightarrow 00:43:38.270$  so it has to get to the nucleus somehow.

NOTE Confidence: 0.886226237142857

00:43:38.270 --> 00:43:40.286 I guess to have its effect

NOTE Confidence: 0.886226237142857

 $00:43:40.286 \longrightarrow 00:43:41.630$  you can get activate.

NOTE Confidence: 0.886226237142857

 $00:43:41.630 \longrightarrow 00:43:42.260$  Outside

NOTE Confidence: 0.930902697142857

 $00:43:42.270 \longrightarrow 00:43:45.180$  of the cells. You don't have to take

NOTE Confidence: 0.930902697142857

 $00:43:45.180 \longrightarrow 00:43:47.280$  anybody to go inside the cells.

NOTE Confidence: 0.786440327826087

 $00:43:48.130 \longrightarrow 00:43:50.176$  Right, but that that but

NOTE Confidence: 0.786440327826087

 $00:43:50.176 \rightarrow 00:43:51.540$  the antibody doesn't necessarily

NOTE Confidence: 0.786440327826087

00:43:51.597 -> 00:43:53.533 take the the drug I guess can get

NOTE Confidence: 0.786440327826087

 $00:43:53.533 \rightarrow 00:43:55.229$  into cells without the antibody,

NOTE Confidence: 0.786440327826087

 $00:43:55.230 \rightarrow 00:43:57.474$  but the reason they conjugated to

NOTE Confidence: 0.786440327826087

 $00{:}43{:}57{.}474 \dashrightarrow 00{:}43{:}59{.}416$  antibodies so you can increase

- NOTE Confidence: 0.786440327826087
- $00:43:59.416 \longrightarrow 00:44:01.684$  the dose locally to the tumor.
- NOTE Confidence: 0.786440327826087
- $00:44:01.690 \longrightarrow 00:44:02.920$  Michael environment.
- NOTE Confidence: 0.786440327826087
- $00:44:02.920 \longrightarrow 00:44:07.240$  We have a more protease type.
- NOTE Confidence: 0.786440327826087
- $00:44:07.240 \longrightarrow 00:44:10.648$  To break up the linkage between
- NOTE Confidence: 0.786440327826087
- $00:44:10.648 \rightarrow 00:44:13.192$  conjugate drug and the conjugate ohh,
- NOTE Confidence: 0.786440327826087
- $00{:}44{:}13.192 \dashrightarrow 00{:}44{:}14.668$  that'd be fine.
- NOTE Confidence: 0.786440327826087
- $00:44:14.668 \longrightarrow 00:44:18.353$  That that that means you read that
- NOTE Confidence: 0.786440327826087
- $00:44:18.353 \rightarrow 00:44:22.656$  could partly explain why the the
- NOTE Confidence: 0.786440327826087
- $00{:}44{:}22.656 \dashrightarrow 00{:}44{:}25.014$  heterogeneity potential difficult
- NOTE Confidence: 0.786440327826087
- 00:44:25.014 --> 00:44:28.706 involvement as well as you may
- NOTE Confidence: 0.786440327826087
- $00:44:28.706 \rightarrow 00:44:31.250$  have another interesting parameter
- NOTE Confidence: 0.786440327826087
- $00:44:31.250 \longrightarrow 00:44:35.938$  to assess now today with the.
- NOTE Confidence: 0.786440327826087
- $00:44:35.940 \longrightarrow 00:44:40.148$  Mass Effect. We could look into.
- NOTE Confidence: 0.786440327826087
- 00:44:40.150 --> 00:44:42.779 Whether they're saying reached?
- NOTE Confidence: 0.786440327826087
- $00:44:42.780 \longrightarrow 00:44:44.520$  Do you conjugate?
- NOTE Confidence: 0.786440327826087

- 00:44:44.520 --> 00:44:44.796 Drugs.
- NOTE Confidence: 0.786440327826087
- $00{:}44{:}44{.}796 \dashrightarrow 00{:}44{:}46{.}452$  And in that case you would
- NOTE Confidence: 0.786440327826087
- $00{:}44{:}46{.}452 \dashrightarrow 00{:}44{:}47{.}760$  argue that it worked.
- NOTE Confidence: 0.786440327826087
- $00{:}44{:}47.760 \dashrightarrow 00{:}44{:}49.345$  It would work without trustors
- NOTE Confidence: 0.786440327826087
- 00:44:49.345 00:44:50.613 maybe even being present.
- NOTE Confidence: 0.786440327826087
- $00{:}44{:}50{.}620 \dashrightarrow 00{:}44{:}52{.}522$  You could you get the deconjugation
- NOTE Confidence: 0.786440327826087
- $00:44:52.522 \rightarrow 00:44:54.739$  even if there's no target present.
- NOTE Confidence: 0.786440327826087
- $00:44:54.740 \longrightarrow 00:44:56.611$  That's that's why you get a negative.
- NOTE Confidence: 0.786440327826087
- 00:44:56.611 --> 00:44:58.837 Right without right without her two
- NOTE Confidence: 0.786440327826087
- $00{:}44{:}58{.}837 \dashrightarrow 00{:}45{:}01{.}641$  present if if the if if it's a true her
- NOTE Confidence: 0.786440327826087
- $00:45:01.641 \longrightarrow 00:45:03.869$  20 the drug could still work because
- NOTE Confidence: 0.786440327826087
- $00:45:03.869 \rightarrow 00:45:06.730$  it could get deconjugation and be effective.
- NOTE Confidence: 0.786440327826087
- $00:45:06.730 \longrightarrow 00:45:09.410$  Everywhere in the body.
- NOTE Confidence: 0.786440327826087
- $00:45:09.410 \dashrightarrow 00:45:12.300$  Anywhere in the exercise room.
- NOTE Confidence: 0.786440327826087
- $00{:}45{:}12{.}300 \dashrightarrow 00{:}45{:}13{.}580$  Have unreached.
- NOTE Confidence: 0.786440327826087
- 00:45:13.580 --> 00:45:14.860 That particular,

- NOTE Confidence: 0.786440327826087
- 00:45:14.860 --> 00:45:15.500 yeah,
- NOTE Confidence: 0.786440327826087
- 00:45:15.500 --> 00:45:16.496 I I think that you know,
- NOTE Confidence: 0.786440327826087
- $00:45:16.500 \longrightarrow 00:45:18.282$  the the question is the toxicity
- NOTE Confidence: 0.786440327826087
- $00{:}45{:}18.282 \dashrightarrow 00{:}45{:}20.150$  then and that's actually the problem.
- NOTE Confidence: 0.786440327826087
- 00:45:20.150 --> 00:45:20.890 I didn't go into that.
- NOTE Confidence: 0.786440327826087
- $00{:}45{:}20.890 \dashrightarrow 00{:}45{:}22.451$  But one of the problems with this
- NOTE Confidence: 0.786440327826087
- $00:45:22.451 \rightarrow 00:45:24.237$  drug is it has pulmonary toxicity
- NOTE Confidence: 0.786440327826087
- $00:45:24.237 \rightarrow 00:45:26.012$  and that patients get interstitial
- NOTE Confidence: 0.786440327826087
- $00{:}45{:}26.012 \dashrightarrow 00{:}45{:}27.938$  lung disease about 10% of the time.
- NOTE Confidence: 0.786440327826087
- $00:45:27.938 \longrightarrow 00:45:29.118$  And that's another reason why
- NOTE Confidence: 0.786440327826087
- 00:45:29.118 --> 00:45:30.708 you need a companion diagnostic.
- NOTE Confidence: 0.786440327826087
- $00{:}45{:}30{.}710 \dashrightarrow 00{:}45{:}33{.}308$  And one wonders if perhaps the
- NOTE Confidence: 0.786440327826087
- $00{:}45{:}33{.}308 \dashrightarrow 00{:}45{:}36{.}069$  interstitial lung disease is due to extra,
- NOTE Confidence: 0.786440327826087
- 00:45:36.070 --> 00:45:37.020 you know,
- NOTE Confidence: 0.786440327826087
- $00{:}45{:}37.020 \dashrightarrow 00{:}45{:}38.920$  extra cellular environment cleaving the
- NOTE Confidence: 0.786440327826087

 $00:45:38.920 \longrightarrow 00:45:42.288$  drug even in the absence of her too,

NOTE Confidence: 0.786440327826087

 $00{:}45{:}42.290 \dashrightarrow 00{:}45{:}43.410$  although we've also found

NOTE Confidence: 0.786440327826087

 $00:45:43.410 \longrightarrow 00:45:44.810$  that her two is present.

NOTE Confidence: 0.786440327826087

 $00:45:44.810 \rightarrow 00:45:47.366$  Normal Airways at about the level it is in,

NOTE Confidence: 0.786440327826087

 $00{:}45{:}47{.}370 \dashrightarrow 00{:}45{:}49{.}379$  low in low in about at about

NOTE Confidence: 0.786440327826087

 $00:45:49.379 \longrightarrow 00:45:51.370 1/4$  UN quote one plus level,

NOTE Confidence: 0.786440327826087

 $00{:}45{:}51{.}370 \dashrightarrow 00{:}45{:}52{.}700$  or between four and six

NOTE Confidence: 0.786440327826087

00:45:52.700 - 00:45:53.764 animals per square millimeter.