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 --> 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 --> 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 --> 00:00:20.674 then came here for for pathology residency

NOTE Confidence: 0.66406729

00:00:20.674 --> 00:00:23.758 and then did a psychopath fellowship

NOTE Confidence: 0.66406729

00:00:23.758 --> 00:00:27.078 at the Medical College of Virginia.

NOTE Confidence: 0.66406729

00:00:27.080 --> 00:00:29.050 He's actually now been at

NOTE Confidence: 0.66406729

00:00:29.050 --> 00:00:31.020 Yale for almost 30 years.

NOTE Confidence: 0.66406729

00:00:31.020 --> 00:00:31.950 That's impressive.

NOTE Confidence: 0.66406729

00:00:31.950 --> 00:00:34.740 He's the director of the Pathology

NOTE Confidence: 0.66406729

00:00:34.740 --> 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 --> 00:00:43.520 at the forefront of.

NOTE Confidence: 0.66406729

00:00:43.520 --> 00:00:46.500 I guess I don't need to as in the

NOTE Confidence: 0.66406729

00:00:46.500 --> 00:00:48.860 forefront 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 --> 00:00:54.794 known throughout the the, the.

NOTE Confidence: 0.66406729

00:00:54.794 --> 00:00:57.218 The field for this he developed

NOTE Confidence: 0.66406729

00:00:57.218 --> 00:00:59.655 many novel assay techniques for

NOTE Confidence: 0.66406729

00:00:59.655 --> 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 --> 00:01:07.210 to which targeted therapies.

NOTE Confidence: 0.66406729

00:01:07.210 --> 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 --> 00:01:12.128 therapies has increased and our

NOTE Confidence: 0.66406729

00:01:12.128 --> 00:01:14.120 use of those drugs has increased.

NOTE Confidence: 0.66406729

00:01:14.120 --> 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 --> 00:01:19.837 for her two directed therapies.

NOTE Confidence: 0.66406729

00:01:19.840 --> 00:01:22.640 I think this is particularly timely as

NOTE Confidence: 0.66406729

00:01:22.640 --> 00:01:26.148 the first her two targeted therapy for non.

NOTE Confidence: 0.66406729

00:01:26.150 --> 00:01:28.075 Fish amplified breast cancers was

NOTE Confidence: 0.66406729

00:01:28.075 --> 00:01:30.754 just approved six months ago and how

NOTE Confidence: 0.66406729

00:01:30.754 --> 00:01:32.464 exactly we identify which patients

NOTE Confidence: 0.66406729

00:01:32.464 --> 00:01:34.846 are going to benefit from this therapy

NOTE Confidence: 0.66406729

00:01:34.846 --> 00:01:37.280 I think is a huge question and the

NOTE Confidence: 0.66406729

00:01:37.280 --> 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 --> 00:01:42.450 and I think he's going to focus on,

NOTE Confidence: 0.66406729

00:01:42.450 --> 00:01:43.782 on on that today.

NOTE Confidence: 0.66406729

00:01:43.782 --> 00:01:45.780 So thank you for bringing this

NOTE Confidence: 0.66406729

00:01:45.859 --> 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 --> 00:01:55.588 the leadership for inviting me today.

NOTE Confidence: 0.838330737692308

00:01:55.590 --> 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 --> 00:01:59.029 He's a world leader in this space

NOTE Confidence: 0.838330737692308

00:01:59.029 --> 00:02:00.370 that I'm going to talk about.

NOTE Confidence: 0.838330737692308

00:02:00.370 --> 00:02:03.520 That is the her two.

NOTE Confidence: 0.838330737692308

00:02:03.520 --> 00:02:06.586 80C or antibody drug conjugate space.

NOTE Confidence: 0.838330737692308

00:02:06.590 --> 00:02:09.159 I'll start by my title is precision

NOTE Confidence: 0.838330737692308

00:02:09.159 --> 00:02:10.967 medicine versus persuasion medicine and

NOTE Confidence: 0.838330737692308

00:02:10.967 --> 00:02:12.887 I'll get to what persuasion medicine

NOTE Confidence: 0.838330737692308

00:02:12.887 --> 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 --> 00:02:20.070 And measuring is what you do quantitatively.

NOTE Confidence: 0.838330737692308

00:02:20.070 --> 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 --> 00:02:25.498 difference between subjective and

NOTE Confidence: 0.838330737692308

00:02:25.498 --> 00:02:27.242 objective assessment of tissue.

NOTE Confidence: 0.939715525

00:02:29.830 --> 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 --> 00:02:38.004 and a lot of the research in my lab,

NOTE Confidence: 0.939715525

00:02:38.010 --> 00:02:39.599 including the work that led to this.

NOTE Confidence: 0.939715525

00:02:39.600 --> 00:02:41.595 Most of what I'm going to present

NOTE Confidence: 0.939715525

00:02:41.595 --> 00:02:43.290 today was sponsored by companies

NOTE Confidence: 0.939715525

00:02:43.290 --> 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 --> 00:02:52.092 minutes or so talking about first and

NOTE Confidence: 0.91608862625

00:02:52.092 --> 00:02:53.580 quick introduction to the new drugs.

NOTE Confidence: 0.91608862625

00:02:53.580 --> 00:02:54.620 If you've heard Ian speak,

NOTE Confidence: 0.91608862625

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

NOTE Confidence: 0.91608862625

00:02:55.740 --> 00:02:58.564 but maybe you didn't a proposed new assay

NOTE Confidence: 0.91608862625

00:02:58.564 --> 00:03:01.117 for these new drugs high sensitivity

NOTE Confidence: 0.91608862625

00:03:01.117 --> 00:03:03.775 would call the assay high sensitivity

NOTE Confidence: 0.91608862625

00:03:03.851 --> 00:03:05.995 or HS or two and then CAP CLIA,

NOTE Confidence: 0.91608862625

00:03:06.000 --> 00:03:08.192 what take, what does it take to get

NOTE Confidence: 0.91608862625

00:03:08.192 --> 00:03:09.791 something from your research lab so

NOTE Confidence: 0.91608862625

00:03:09.791 --> 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 --> 00:03:15.378 results in the patient's chart.

NOTE Confidence: 0.91608862625

00:03:15.378 --> 00:03:17.650 That's what cap CLIA is taking the new.

NOTE Confidence: 0.91608862625

00:03:17.650 --> 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 --> 00:03:23.047 persuasion medicine and try to talk all

NOTE Confidence: 0.91608862625

00:03:23.103 --> 00:03:24.775 of you who are oncologists in the room

NOTE Confidence: 0.91608862625

00:03:24.775 --> 00:03:26.656 and to not using persuasion medicine

NOTE Confidence: 0.91608862625

00:03:26.656 --> 00:03:28.476 and focusing on precision medicine.

NOTE Confidence: 0.805516176666667

00:03:30.610 --> 00:03:32.869 So this is the, the big drug that got

NOTE Confidence: 0.805516176666667

00:03:32.869 --> 00:03:35.139 the first standing ovation in 25 years

NOTE Confidence: 0.805516176666667

00:03:35.139 --> 00:03:37.710 as I understand at ASCO and it it's,

NOTE Confidence: 0.805516176666667

00:03:37.710 --> 00:03:39.310 it's the same old drug,

NOTE Confidence: 0.805516176666667

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

NOTE Confidence: 0.805516176666667

00:03:41.116 --> 00:03:44.026 but they've conjugated 8 topoisomerase

NOTE Confidence: 0.805516176666667

00:03:44.026 --> 00:03:47.002 inhibitor payloads to the trastuzumab that

NOTE Confidence: 0.805516176666667

00:03:47.002 --> 00:03:49.850 gives you especially some special tricks.

NOTE Confidence: 0.805516176666667

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

NOTE Confidence: 0.805516176666667

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

NOTE Confidence: 0.805516176666667

00:03:53.330 --> 00:03:55.738 So it doesn't have the toxicity that

NOTE Confidence: 0.805516176666667

00:03:55.738 --> 00:03:58.092 giving the drug and the dosages that

NOTE Confidence: 0.805516176666667

00:03:58.092 --> 00:04:00.274 it would be given cause would cause.

NOTE Confidence: 0.805516176666667

00:04:00.274 --> 00:04:01.506 All kinds of toxicity.

NOTE Confidence: 0.805516176666667

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

NOTE Confidence: 0.805516176666667

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

NOTE Confidence: 0.805516176666667

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

NOTE Confidence: 0.805516176666667

00:04:07.450 --> 00:04:09.052 when it gets uncoupled in the

NOTE Confidence: 0.805516176666667

00:04:09.052 --> 00:04:11.406 cell it can spill out of the cell

NOTE Confidence: 0.805516176666667

00:04:11.406 --> 00:04:12.630 and kill neighboring cells.

NOTE Confidence: 0.805516176666667

00:04:12.630 --> 00:04:15.558 The so the the sort of neighborhood effect

NOTE Confidence: 0.805516176666667

00:04:15.558 --> 00:04:19.730 or proximity effect of the therapy.

NOTE Confidence: 0.805516176666667

00:04:19.730 --> 00:04:21.464 It worked really well and that's

NOTE Confidence: 0.805516176666667

00:04:21.464 --> 00:04:23.458 why we've all heard about it that

NOTE Confidence: 0.805516176666667

00:04:23.458 --> 00:04:25.768 you can see very few patients were

NOTE Confidence: 0.805516176666667

00:04:25.768 --> 00:04:27.458 resistant but most patients had

NOTE Confidence: 0.805516176666667

00:04:27.458 --> 00:04:29.490 some response and there were eleven

NOTE Confidence: 0.805516176666667

00:04:29.490 --> 00:04:32.492 CR's in the early trials and in

NOTE Confidence: 0.805516176666667

00:04:32.492 --> 00:04:34.809 fact it worked at for all patients,

NOTE Confidence: 0.805516176666667

00:04:34.810 --> 00:04:36.390 but especially in patients that

NOTE Confidence: 0.805516176666667

00:04:36.390 --> 00:04:38.250 were not amplified for her too.

NOTE Confidence: 0.805516176666667

00:04:38.250 --> 00:04:40.126 So the initial trials were all in

NOTE Confidence: 0.805516176666667

00:04:40.126 --> 00:04:42.149 patients that had her two amplification,

NOTE Confidence: 0.805516176666667

00:04:42.150 --> 00:04:44.004 but then they started trials on

NOTE Confidence: 0.805516176666667

00:04:44.004 --> 00:04:45.979 patients with low her two IHC 2

NOTE Confidence: 0.805516176666667

00:04:45.979 --> 00:04:47.970 plus and HC1 plus and you can see

NOTE Confidence: 0.805516176666667

00:04:47.970 --> 00:04:49.670 the curves look pretty similar.

NOTE Confidence: 0.805516176666667

00:04:49.670 --> 00:04:51.236 And in fact in those low,

NOTE Confidence: 0.805516176666667

00:04:51.240 --> 00:04:53.557 low patients in the Destiny 4 trial,

NOTE Confidence: 0.805516176666667

00:04:53.560 --> 00:04:54.884 ultimately the survival curve

NOTE Confidence: 0.805516176666667

00:04:54.884 --> 00:04:56.756 looks like great, looks like this,

NOTE Confidence: 0.805516176666667

00:04:56.756 --> 00:04:58.508 which is really a great improvement

NOTE Confidence: 0.805516176666667

00:04:58.508 --> 00:05:00.584 in the survival curve for advanced

NOTE Confidence: 0.805516176666667

00:05:00.584 --> 00:05:02.309 breast cancer and changing median

NOTE Confidence: 0.805516176666667

00:05:02.370 --> 00:05:03.858 survival from 5 to 9 months.

NOTE Confidence: 0.805516176666667

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

NOTE Confidence: 0.805516176666667

00:05:06.512 --> 00:05:09.228 has led to the popularization of this

NOTE Confidence: 0.805516176666667

00:05:09.228 --> 00:05:11.440 drug and the success of the drug.

NOTE Confidence: 0.805516176666667

00:05:11.440 --> 00:05:13.342 And they said we concluded a

NOTE Confidence: 0.805516176666667

00:05:13.342 --> 00:05:15.272 randomized 2 group open label phase

NOTE Confidence: 0.805516176666667

00:05:15.272 --> 00:05:17.054 two trial with her too low.

NOTE Confidence: 0.805516176666667

00:05:17.060 --> 00:05:18.144 What does that mean?

NOTE Confidence: 0.805516176666667

00:05:18.144 --> 00:05:20.244 So that's what we'll examine the rest, but.

NOTE Confidence: 0.805516176666667

00:05:20.244 --> 00:05:20.900 Before we go there,

NOTE Confidence: 0.805516176666667

00:05:20.900 --> 00:05:22.036 what about her 20?

NOTE Confidence: 0.805516176666667

00:05:22.036 --> 00:05:23.740 What about if they don't express

NOTE Confidence: 0.805516176666667

00:05:23.796 --> 00:05:25.695 any her two at all and can we tell

NOTE Confidence: 0.805516176666667

00:05:25.695 --> 00:05:27.302 the difference between her 20 and

NOTE Confidence: 0.805516176666667

00:05:27.302 --> 00:05:29.580 her two low and in fact in her two

NOTE Confidence: 0.805516176666667

00:05:29.580 --> 00:05:31.353 zeros and this there is a trial

NOTE Confidence: 0.805516176666667

00:05:31.353 --> 00:05:33.177 going underway that's her two less

NOTE Confidence: 0.805516176666667

00:05:33.177 --> 00:05:35.179 than one but greater than zero.

NOTE Confidence: 0.805516176666667

00:05:35.180 --> 00:05:36.690 That's the Destiny 6 trial

NOTE Confidence: 0.805516176666667

00:05:36.690 --> 00:05:37.596 hasn't reported yet.

NOTE Confidence: 0.805516176666667

00:05:37.600 --> 00:05:39.832 But there's also the her 20 equal 0

NOTE Confidence: 0.805516176666667

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

NOTE Confidence: 0.805516176666667

00:05:41.912 --> 00:05:43.843 in France where there was clearly

NOTE Confidence: 0.805516176666667

00:05:43.843 --> 00:05:45.893 in these waterfall plots clearly

NOTE Confidence: 0.805516176666667

00:05:45.893 --> 00:05:47.884 patients that benefited from drug

NOTE Confidence: 0.805516176666667

00:05:47.884 --> 00:05:50.980 even though they had a hurt 2 = 0.

NOTE Confidence: 0.805516176666667

00:05:50.980 --> 00:05:53.052 So is this the why is it important

NOTE Confidence: 0.805516176666667

00:05:53.052 --> 00:05:54.816 to understand this and have good

NOTE Confidence: 0.805516176666667

00:05:54.816 --> 00:05:56.301 diagnostics for it because this

NOTE Confidence: 0.805516176666667

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

NOTE Confidence: 0.805516176666667

00:05:58.060 --> 00:05:59.476 Here's a list of other drugs

NOTE Confidence: 0.805516176666667

00:05:59.476 --> 00:06:01.100 which there's no way you can read,

NOTE Confidence: 0.805516176666667

00:06:01.100 --> 00:06:02.396 but all of these drugs are,

NOTE Confidence: 0.805516176666667

00:06:02.400 --> 00:06:04.380 are all these are targets for

NOTE Confidence: 0.805516176666667

00:06:04.380 --> 00:06:05.784 ADC's in clinical trials.

NOTE Confidence: 0.805516176666667

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

NOTE Confidence: 0.805516176666667

00:06:08.016 --> 00:06:09.780 important for oncology in the next

NOTE Confidence: 0.861392332

00:06:09.835 --> 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 --> 00:06:15.149 actually pick the right patients as

NOTE Confidence: 0.861392332

00:06:15.149 --> 00:06:16.840 opposed to giving the drug because

NOTE Confidence: 0.861392332

00:06:16.840 --> 00:06:18.800 unlike when we know the tiger it so

NOTE Confidence: 0.861392332

00:06:18.852 --> 00:06:20.684 well and we know how the drug works.

NOTE Confidence: 0.861392332

00:06:20.690 --> 00:06:22.237 It's really important to be able to

NOTE Confidence: 0.861392332

00:06:22.237 --> 00:06:23.893 pick the right target or to pick

NOTE Confidence: 0.861392332

00:06:23.893 --> 00:06:25.068 the right patients that express

NOTE Confidence: 0.861392332

00:06:25.068 --> 00:06:26.369 the right amount of target.

NOTE Confidence: 0.861392332

00:06:26.370 --> 00:06:27.390 So what do we do now?

NOTE Confidence: 0.861392332

00:06:27.390 --> 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 --> 00:06:35.106 these guidelines are how we practice

NOTE Confidence: 0.861392332

00:06:35.106 --> 00:06:36.850 as pathologists in assessment

NOTE Confidence: 0.861392332

00:06:36.924 --> 00:06:38.380 of her two expression.

NOTE Confidence: 0.861392332

00:06:38.380 --> 00:06:41.220 And this is the algorithm for what

NOTE Confidence: 0.861392332

00:06:41.220 --> 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 --> 00:06:47.517 intense and greater than 10% of the cells.

NOTE Confidence: 0.861392332

00:06:47.517 --> 00:06:48.712 That makes the three plus

NOTE Confidence: 0.861392332

00:06:48.712 --> 00:06:50.139 and then we have a 2 + 1 +.

NOTE Confidence: 0.861392332

00:06:50.140 --> 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 --> 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 --> 00:06:59.551 1 is faint partial membrane staining

NOTE Confidence: 0.861392332

00:06:59.551 --> 00:07:02.360 and weak to moderate staining is +2.

NOTE Confidence: 0.861392332

00:07:02.360 --> 00:07:04.898 That's kind of subjective. In fact.

NOTE Confidence: 0.861392332

00:07:04.900 --> 00:07:06.538 How well can we do that and

NOTE Confidence: 0.861392332

00:07:06.538 --> 00:07:07.460 how important is it?

NOTE Confidence: 0.861392332

00:07:07.460 --> 00:07:07.754 Well.

NOTE Confidence: 0.861392332

00:07:07.754 --> 00:07:09.812 It used to be important to tell

NOTE Confidence: 0.861392332

00:07:09.812 --> 00:07:11.743 the heart threes the 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 --> 00:07:15.729 two pluses were they the reflex.

NOTE Confidence: 0.861392332

00:07:15.730 --> 00:07:17.578 But now it's important to have this CAD.

NOTE Confidence: 0.861392332

00:07:17.580 --> 00:07:19.589 The new category is far too low.

NOTE Confidence: 0.861392332

00:07:19.590 --> 00:07:20.530 And how many are there?

NOTE Confidence: 0.861392332

00:07:20.530 --> 00:07:21.634 There's a lot,

NOTE Confidence: 0.861392332

00:07:21.634 --> 00:07:24.525 maybe as many as 65 or 70% of the

NOTE Confidence: 0.861392332

00:07:24.525 --> 00:07:26.890 patients are thought to fall into this low,

NOTE Confidence: 0.861392332

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

NOTE Confidence: 0.861392332

00:07:28.390 --> 00:07:30.190 a lot of patients could get drug,

NOTE Confidence: 0.861392332

00:07:30.190 --> 00:07:31.999 but it also means that we need to be

NOTE Confidence: 0.861392332

00:07:31.999 --> 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 --> 00:07:37.576 the her two zeros to get the drug

NOTE Confidence: 0.861392332

00:07:37.580 --> 00:07:38.756 if they aren't going to benefit.

NOTE Confidence: 0.861392332

00:07:38.760 --> 00:07:39.856 Well, maybe we do.

NOTE Confidence: 0.861392332

00:07:39.856 --> 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 --> 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 --> 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 --> 00:07:50.406 the College of American Pathologists.

NOTE Confidence: 0.861392332

00:07:50.410 --> 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 --> 00:07:54.620 what CLIA labs are.

NOTE Confidence: 0.861392332

00:07:54.620 --> 00:07:55.070 That is,

NOTE Confidence: 0.861392332

00:07:55.070 --> 00:07:56.862 for a CLIA lab or clinical lab

NOTE Confidence: 0.861392332

00:07:56.862 --> 00:07:58.428 to return data to the chart,

NOTE Confidence: 0.861392332

00:07:58.430 --> 00:08:00.038 they have to do a survey twice a

NOTE Confidence: 0.861392332

00:08:00.038 --> 00:08:01.724 year to show that they're competent

NOTE Confidence: 0.861392332

00:08:01.724 --> 00:08:03.566 and effective at doing the assay.

NOTE Confidence: 0.861392332

00:08:03.570 --> 00:08:05.838 And here's the surveys for anatomic

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 --> 00:08:11.030 microarray. This is her to a 2020.

NOTE Confidence: 0.861392332

00:08:11.030 --> 00:08:12.974 So it was the fall survey or the

NOTE Confidence: 0.861392332

00:08:12.974 --> 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 --> 00:08:18.148 And you can see my colleagues here,

NOTE Confidence: 0.861392332

00:08:18.150 --> 00:08:20.005 including myself, who are on this committee.

NOTE Confidence: 0.861392332

00:08:20.010 --> 00:08:21.697 And when we looked at these surveys,

NOTE Confidence: 0.861392332

00:08:21.700 --> 00:08:23.765 we noticed that four, six and seven,

NOTE Confidence: 0.861392332

00:08:23.770 --> 00:08:26.770 that is 3 out of 10 did not reach consensus.

NOTE Confidence: 0.861392332

00:08:26.770 --> 00:08:29.382 That means that of the 1400 labs

NOTE Confidence: 0.861392332

00:08:29.382 --> 00:08:31.750 in the in the world that did this,

NOTE Confidence: 0.861392332

00:08:31.750 --> 00:08:33.898 they couldn't come to an agreement.

NOTE Confidence: 0.861392332

00:08:33.900 --> 00:08:34.362 That is,

NOTE Confidence: 0.861392332

00:08:34.362 --> 00:08:35.517 you need to have 90%

NOTE Confidence: 0.898946901666667

00:08:35.520 --> 00:08:37.164 consensus to have agreement.

NOTE Confidence: 0.898946901666667

00:08:37.164 --> 00:08:38.758 In fact, if we look at this one,

NOTE Confidence: 0.898946901666667

00:08:38.760 --> 00:08:39.364 it's interesting.

NOTE Confidence: 0.898946901666667

00:08:39.364 --> 00:08:41.780 This is one of the cases that didn't

NOTE Confidence: 0.898946901666667

00:08:41.841 --> 00:08:43.521 come to agreement and that was

NOTE Confidence: 0.898946901666667

00:08:43.521 --> 00:08:45.259 because there was a big discordance

NOTE Confidence: 0.898946901666667

00:08:45.259 --> 00:08:47.219 in the number of called 0 versus

NOTE Confidence: 0.898946901666667

00:08:47.219 --> 00:08:48.826 1 and there were a fair number

NOTE Confidence: 0.898946901666667

00:08:48.826 --> 00:08:50.360 that even called it two or three.

NOTE Confidence: 0.898946901666667

00:08:50.360 --> 00:08:51.335 So that's troublesome.

NOTE Confidence: 0.898946901666667

00:08:51.335 --> 00:08:54.003 If we're testing these labs twice a year

NOTE Confidence: 0.898946901666667

00:08:54.003 --> 00:08:56.019 and we're assuring that they're giving

NOTE Confidence: 0.898946901666667

00:08:56.019 --> 00:08:58.038 the right answer for the patients,

NOTE Confidence: 0.898946901666667

00:08:58.040 --> 00:09:00.147 how can you have that much difference

NOTE Confidence: 0.898946901666667

00:09:00.147 --> 00:09:02.559 between zero and one that it's almost 5050.

NOTE Confidence: 0.898946901666667

00:09:02.560 --> 00:09:05.440 So since I I'm on the CAP committee,

NOTE Confidence: 0.898946901666667

00:09:05.440 --> 00:09:06.945 I could ask for the data from

NOTE Confidence: 0.898946901666667

00:09:06.945 --> 00:09:07.950 the last few years.

NOTE Confidence: 0.898946901666667

00:09:07.950 --> 00:09:09.485 And here's the data from

NOTE Confidence: 0.898946901666667

00:09:09.485 --> 00:09:11.655 the lab from 2019 and 2020.

NOTE Confidence: 0.898946901666667

00:09:11.655 --> 00:09:13.730 And of the 80 cases,

NOTE Confidence: 0.898946901666667

00:09:13.730 --> 00:09:15.698 fifteen of those cases showed a

NOTE Confidence: 0.898946901666667

00:09:15.698 --> 00:09:17.329 discordance of greater than 25%.

NOTE Confidence: 0.898946901666667

00:09:17.329 --> 00:09:19.243 And that's shown in these pie

NOTE Confidence: 0.898946901666667

00:09:19.243 --> 00:09:21.063 charts here where the zeros are

NOTE Confidence: 0.898946901666667

00:09:21.063 --> 00:09:22.911 blue and the ones are red and

NOTE Confidence: 0.898946901666667

00:09:22.978 --> 00:09:25.066 anything higher than one is black.

NOTE Confidence: 0.898946901666667

00:09:25.070 --> 00:09:25.640 Two and three,

NOTE Confidence: 0.898946901666667

00:09:25.640 --> 00:09:27.210 since we're not going to focus on that.

NOTE Confidence: 0.898946901666667

00:09:27.210 --> 00:09:28.154 So we we did,

NOTE Confidence: 0.898946901666667

00:09:28.154 --> 00:09:30.056 we thought is this really, you know,

NOTE Confidence: 0.898946901666667

00:09:30.056 --> 00:09:31.130 this is concerning,

NOTE Confidence: 0.898946901666667

00:09:31.130 --> 00:09:33.106 but you know what this is tissue microarrays.

NOTE Confidence: 0.898946901666667

00:09:33.110 --> 00:09:34.982 This is not what happens in the real world.

NOTE Confidence: 0.898946901666667

00:09:34.990 --> 00:09:37.078 So then we did a study of real

NOTE Confidence: 0.898946901666667

00:09:37.078 --> 00:09:38.240 world core biopsies.

NOTE Confidence: 0.898946901666667

00:09:38.240 --> 00:09:40.352 And enrolled 18 pathologists from 15

NOTE Confidence: 0.898946901666667

00:09:40.352 --> 00:09:42.092 institutions around the United States

NOTE Confidence: 0.898946901666667

00:09:42.092 --> 00:09:44.038 and ask them to read actual core

NOTE Confidence: 0.898946901666667

00:09:44.038 --> 00:09:45.856 biopsies that have been read at Yale.

NOTE Confidence: 0.898946901666667

00:09:45.860 --> 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: 0.898946901666667

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

NOTE Confidence: 0.898946901666667

00:09:53.638 --> 00:09:55.275 publication and the popularization

NOTE Confidence: 0.898946901666667

00:09:55.275 --> 00:09:57.858 of her two one plus versus 0.

NOTE Confidence: 0.898946901666667

00:09:57.860 --> 00:09:59.652 So they didn't know they were just

NOTE Confidence: 0.898946901666667

00:09:59.652 --> 00:10:01.384 doing the ASCO CAP guidelines as

NOTE Confidence: 0.898946901666667

00:10:01.384 --> 00:10:03.593 they always have, and scoring 0123.

NOTE Confidence: 0.898946901666667

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

NOTE Confidence: 0.898946901666667

00:10:05.320 --> 00:10:07.056 what they're scoring looked like was this.

NOTE Confidence: 0.898946901666667

00:10:07.060 --> 00:10:08.467 That is, the Blues were the zeros.

NOTE Confidence: 0.898946901666667

00:10:08.470 --> 00:10:10.468 This is the percent of pathologists.

NOTE Confidence: 0.898946901666667

00:10:10.470 --> 00:10:11.894 That scored at 0,

NOTE Confidence: 0.898946901666667

00:10:11.894 --> 00:10:14.030 so a fair number agreed that

NOTE Confidence: 0.898946901666667

00:10:14.030 --> 00:10:15.438 that there were zeros.

NOTE Confidence: 0.898946901666667

00:10:15.438 --> 00:10:18.370 There were 92 cases that were discordant,

NOTE Confidence: 0.898946901666667

00:10:18.370 --> 00:10:19.822 and of those,

NOTE Confidence: 0.898946901666667

00:10:19.822 --> 00:10:23.210 9269 were discordant between zero and one,

NOTE Confidence: 0.898946901666667

00:10:23.210 --> 00:10:24.875 and only twenty were discordant

NOTE Confidence: 0.898946901666667

00:10:24.875 --> 00:10:26.207 between 2:00 and 3:00.

NOTE Confidence: 0.898946901666667

00:10:26.210 --> 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: 0.898946901666667

00:10:34.460 --> 00:10:35.978 How come it's not advancing now?

NOTE Confidence: 0.85056264125

00:10:38.430 --> 00:10:43.566 Oh, hold on. I lost my laser pointer.

NOTE Confidence: 0.85056264125

00:10:43.570 --> 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 --> 00:10:48.530 Gray as it's saying restart.

NOTE Confidence: 0.85056264125

00:10:48.530 --> 00:10:49.643 I probably shouldn't.

NOTE Confidence: 0.85056264125

00:10:49.643 --> 00:10:51.498 I should probably wait for

NOTE Confidence: 0.85056264125

00:10:51.498 --> 00:10:52.989 the program to respond.

NOTE Confidence: 0.85056264125

00:10:52.990 --> 00:10:54.194 Very sorry about this,

NOTE Confidence: 0.85056264125

00:10:54.194 --> 00:10:56.627 but suffice it to say that I'll skip

NOTE Confidence: 0.85056264125

00:10:56.627 --> 00:10:58.883 the next slide so we can keep going.

NOTE Confidence: 0.85056264125

00:10:58.890 --> 00:11:00.400 The next slide was after

NOTE Confidence: 0.85056264125

00:11:00.400 --> 00:11:01.910 many review rounds of review,

NOTE Confidence: 0.85056264125

00:11:01.910 --> 00:11:03.750 we did get this published in JAMA Oncology,

NOTE Confidence: 0.85056264125

00:11:03.750 --> 00:11:04.890 but weren't allowed to say

NOTE Confidence: 0.85056264125

00:11:04.890 --> 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 --> 00:11:09.462 great discordance between zero and

NOTE Confidence: 0.85056264125

00:11:09.462 --> 00:11:11.052 one and not so much discordance

NOTE Confidence: 0.85056264125

00:11:11.052 --> 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 --> 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 --> 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 --> 00:11:28.076 Wait to respond or restart the program.

NOTE Confidence: 0.865999128571429

00:11:28.080 --> 00:11:29.494 Maybe I should restart the program and

NOTE Confidence: 0.865999128571429

00:11:29.494 --> 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 --> 00:11:36.560 the computer, it's just. Yeah.

NOTE Confidence: 0.914624506666667

00:11:36.560 --> 00:11:40.718 Let's try again. Yeah, we're good.

NOTE Confidence: 0.914624506666667

00:11:40.718 --> 00:11:43.094 We're good. Sorry about that. OK.

NOTE Confidence: 0.914624506666667

00:11:43.094 --> 00:11:45.350 We saw all those things already.

NOTE Confidence: 0.914624506666667

00:11:45.350 --> 00:11:49.480 Let's go to. The study that was in

NOTE Confidence: 0.914624506666667

00:11:49.480 --> 00:11:51.768 JAMA Oncology was here and this is

NOTE Confidence: 0.914624506666667

00:11:51.768 --> 00:11:54.261 what was the this is the figure and

NOTE Confidence: 0.914624506666667

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

NOTE Confidence: 0.914624506666667

00:11:56.367 --> 00:11:58.726 on this study in my lab and she.

NOTE Confidence: 0.914624506666667

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

NOTE Confidence: 0.914624506666667

00:12:00.480 --> 00:12:02.385 that shows that there's a lot more

NOTE Confidence: 0.914624506666667

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

NOTE Confidence: 0.914624506666667

00:12:03.760 --> 00:12:05.605 than there is between 2:00 and 3:00.

NOTE Confidence: 0.914624506666667

00:12:05.610 --> 00:12:07.605 And for two we have a solution.

NOTE Confidence: 0.914624506666667

00:12:07.610 --> 00:12:09.050 For two we can do fish,

NOTE Confidence: 0.914624506666667

00:12:09.050 --> 00:12:10.970 so we have a orthogonal assay.

NOTE Confidence: 0.914624506666667

00:12:10.970 --> 00:12:12.474 What do we do between zero and one?

NOTE Confidence: 0.914624506666667

00:12:12.480 --> 00:12:14.160 Well, we don't have a solution yet.

NOTE Confidence: 0.914624506666667

00:12:14.160 --> 00:12:15.904 That's what I'll show you in a minute.

NOTE Confidence: 0.914624506666667

00:12:15.910 --> 00:12:18.694 But also you can look at this analysis

NOTE Confidence: 0.914624506666667

00:12:18.694 --> 00:12:21.286 which which shows you this is a work

NOTE Confidence: 0.914624506666667

00:12:21.286 --> 00:12:24.221 done by Jack Robbins in the lab with

NOTE Confidence: 0.914624506666667

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

NOTE Confidence: 0.914624506666667

00:12:26.120 --> 00:12:29.080 of people that called 0 versus called one.

NOTE Confidence: 0.914624506666667

00:12:29.080 --> 00:12:30.886 And so if your pathologist #18 and

NOTE Confidence: 0.914624506666667

00:12:30.886 --> 00:12:32.772 these are all currently signing out

NOTE Confidence: 0.914624506666667

00:12:32.772 --> 00:12:34.872 pathologists most with more than five

NOTE Confidence: 0.914624506666667

00:12:34.872 --> 00:12:37.056 years of experience around the country.

NOTE Confidence: 0.914624506666667

00:12:37.060 --> 00:12:39.274 So these are not residents or not to say

NOTE Confidence: 0.914624506666667

00:12:39.274 --> 00:12:41.599 that residents can't do this just as well.

NOTE Confidence: 0.914624506666667

00:12:41.600 --> 00:12:43.365 But these are not residents

NOTE Confidence: 0.914624506666667

00:12:43.365 --> 00:12:44.777 or or or laboratorians.

NOTE Confidence: 0.914624506666667

00:12:44.780 --> 00:12:46.640 These are sign up with ologists.

NOTE Confidence: 0.914624506666667

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

NOTE Confidence: 0.914624506666667

00:12:48.999 --> 00:12:51.657 score 15% of the patients with a 0,

NOTE Confidence: 0.914624506666667

00:12:51.660 --> 00:12:53.040 but if your pathologist number one,

NOTE Confidence: 0.914624506666667

00:12:53.040 --> 00:12:54.090 you have 44%.

NOTE Confidence: 0.914624506666667

00:12:54.090 --> 00:12:56.540 So whether or not you get trustors,

NOTE Confidence: 0.914624506666667

00:12:56.540 --> 00:12:57.130 mab drugs,

NOTE Confidence: 0.914624506666667

00:12:57.130 --> 00:12:59.195 tecan depends on who your pathologist is.

NOTE Confidence: 0.914624506666667

00:12:59.200 --> 00:13:01.846 That doesn't sound like a great idea to me.

NOTE Confidence: 0.914624506666667

00:13:01.850 --> 00:13:03.810 So what we asked is how many people

NOTE Confidence: 0.914624506666667

00:13:03.810 --> 00:13:05.760 do you need to make sure that

NOTE Confidence: 0.914624506666667

00:13:05.760 --> 00:13:07.570 an assay agrees with each other?

NOTE Confidence: 0.914624506666667

00:13:07.570 --> 00:13:09.826 And we, we invented this with gang hand.

NOTE Confidence: 0.914624506666667

00:13:09.830 --> 00:13:12.630 We invented this system to realize that

NOTE Confidence: 0.914624506666667

00:13:12.630 --> 00:13:14.415 there's 21,000 pathologists just in the

NOTE Confidence: 0.914624506666667

00:13:14.415 --> 00:13:17.027 US and at that and 100,000 in the world.

NOTE Confidence: 0.914624506666667

00:13:17.030 --> 00:13:18.806 So how many do we need to decide

NOTE Confidence: 0.914624506666667

00:13:18.806 --> 00:13:20.389 whether or not an essay is good?

NOTE Confidence: 0.914624506666667

00:13:20.390 --> 00:13:22.581 And so we there, there is actually

NOTE Confidence: 0.914624506666667

00:13:22.581 --> 00:13:24.089 no statistical method for this.

NOTE Confidence: 0.914624506666667

00:13:24.090 --> 00:13:26.334 So we simply decided to plot

NOTE Confidence: 0.914624506666667

00:13:26.334 --> 00:13:27.830 the overall percent agreement.

NOTE Confidence: 0.914624506666667

00:13:27.830 --> 00:13:30.116 That's what overall LPA stands for

NOTE Confidence: 0.914624506666667

00:13:30.116 --> 00:13:32.240 versus the observers or readers.

NOTE Confidence: 0.914624506666667

00:13:32.240 --> 00:13:34.728 And what you see is that the more

NOTE Confidence: 0.914624506666667

00:13:34.728 --> 00:13:35.750 observers you have,

NOTE Confidence: 0.914624506666667

00:13:35.750 --> 00:13:36.870 the less agreement you have,

NOTE Confidence: 0.914624506666667

00:13:36.870 --> 00:13:37.533 which makes sense.

NOTE Confidence: 0.914624506666667

00:13:37.533 --> 00:13:38.638 The more people you ask,

NOTE Confidence: 0.914624506666667

00:13:38.640 --> 00:13:39.592 the more discordance you're

NOTE Confidence: 0.914624506666667

00:13:39.592 --> 00:13:41.020 going to get in your answers,

NOTE Confidence: 0.914624506666667

00:13:41.020 --> 00:13:42.154 just mathematical truism.

NOTE Confidence: 0.914624506666667

00:13:42.154 --> 00:13:44.800 And so does this actually work and

NOTE Confidence: 0.914624506666667

00:13:44.873 --> 00:13:47.015 can this be used to assess assays?

NOTE Confidence: 0.914624506666667

00:13:47.020 --> 00:13:48.256 So here's estrogen receptor.

NOTE Confidence: 0.914624506666667

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

NOTE Confidence: 0.914624506666667

00:13:49.801 --> 00:13:51.110 at estrogen receptor.

NOTE Confidence: 0.914624506666667

00:13:51.110 --> 00:13:53.876 If you have a quartet of

NOTE Confidence: 0.914624506666667

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

NOTE Confidence: 0.914624506666667

00:13:55.720 --> 00:13:58.100 all four of them will agree somewhere

NOTE Confidence: 0.914624506666667

00:13:58.100 --> 00:14:01.000 between 85 and 95% of the time.

NOTE Confidence: 0.914624506666667

00:14:01.000 --> 00:14:01.798 How do we do for her?

NOTE Confidence: 0.914624506666667

00:14:01.800 --> 00:14:05.040 Too well, not so well.

NOTE Confidence: 0.914624506666667

00:14:05.040 --> 00:14:06.378 This is the plot for her.

NOTE Confidence: 0.914624506666667

00:14:06.380 --> 00:14:07.760 2/3 plus or not three plus.

NOTE Confidence: 0.914624506666667

00:14:07.760 --> 00:14:09.340 We're really good at that.

NOTE Confidence: 0.914624506666667

00:14:09.340 --> 00:14:12.060 But if you have a quartet of pathologists

NOTE Confidence: 0.914624506666667

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

NOTE Confidence: 0.914624506666667

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

NOTE Confidence: 0.902744163636364

00:14:17.880 --> 00:14:19.665 85%. So this is a new method

NOTE Confidence: 0.902744163636364

00:14:19.665 --> 00:14:21.020 to approach the analysis,

NOTE Confidence: 0.902744163636364

00:14:21.020 --> 00:14:22.612 to try to figure out how many we

NOTE Confidence: 0.902744163636364

00:14:22.612 --> 00:14:24.382 need and how many do we need to make

NOTE Confidence: 0.902744163636364

00:14:24.382 --> 00:14:26.016 a new assay to make a good study.

NOTE Confidence: 0.902744163636364

00:14:26.020 --> 00:14:27.220 Well, it's when it plateaus,

NOTE Confidence: 0.902744163636364

00:14:27.220 --> 00:14:29.620 so in this case we probably need 9 or 10.

NOTE Confidence: 0.902744163636364

00:14:29.620 --> 00:14:31.461 And this case, no number is sufficient

NOTE Confidence: 0.902744163636364

00:14:31.461 --> 00:14:33.617 because it goes all the way down to the

NOTE Confidence: 0.902744163636364

00:14:33.617 --> 00:14:35.592 baseline to tell ones from, not once.

NOTE Confidence: 0.902744163636364

00:14:35.592 --> 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 --> 00:14:42.619 you that we need a new assay.

NOTE Confidence: 0.902744163636364

00:14:42.620 --> 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 --> 00:14:50.490 not red. And so based on that.

NOTE Confidence: 0.902744163636364

00:14:50.490 --> 00:14:52.464 We start, we started from the beginning

NOTE Confidence: 0.902744163636364

00:14:52.464 --> 00:14:54.347 with cell lines and these cell lines

NOTE Confidence: 0.902744163636364

00:14:54.347 --> 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 --> 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 --> 00:15:02.582 but are not gene amplified and

NOTE Confidence: 0.902744163636364

00:15:02.582 --> 00:15:04.646 you can see when you plot them.

NOTE Confidence: 0.902744163636364

00:15:04.650 --> 00:15:06.876 If you look with the current FDA

NOTE Confidence: 0.902744163636364

00:15:06.876 --> 00:15:08.863 approved assay you can separate the

NOTE Confidence: 0.902744163636364

00:15:08.863 --> 00:15:11.290 highs from the lows or the negatives,

NOTE Confidence: 0.902744163636364

00:15:11.290 --> 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 --> 00:15:18.122 pretty simple new assay.

NOTE Confidence: 0.902744163636364

00:15:18.122 --> 00:15:20.382 You can then stratify the low cell

NOTE Confidence: 0.902744163636364

00:15:20.382 --> 00:15:22.686 lines and tell the zeros from the ones.

NOTE Confidence: 0.902744163636364

00:15:22.690 --> 00:15:24.892 Essentially if you were reading the

NOTE Confidence: 0.902744163636364

00:15:24.892 --> 00:15:27.110 cell lines but it was the wrong,

NOTE Confidence: 0.902744163636364

00:15:27.110 --> 00:15:28.952 the wrong the current assay is

NOTE Confidence: 0.902744163636364

00:15:28.952 --> 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 --> 00:15:37.558 The current assay now FDA approved,

NOTE Confidence: 0.902744163636364

00:15:37.560 --> 00:15:39.570 is like weighing mice on a

NOTE Confidence: 0.902744163636364

00:15:39.570 --> 00:15:40.575 scale for elephants.

NOTE Confidence: 0.902744163636364

00:15:40.580 --> 00:15:42.540 And I think this is really good

NOTE Confidence: 0.902744163636364

00:15:42.540 --> 00:15:43.941 because everybody gets this if

NOTE Confidence: 0.902744163636364

00:15:43.941 --> 00:15:45.459 you have a skill for elephants,

NOTE Confidence: 0.902744163636364

00:15:45.460 --> 00:15:47.722 it doesn't work for weighing mice

NOTE Confidence: 0.902744163636364

00:15:47.722 --> 00:15:50.320 and it's all about dynamic range.

NOTE Confidence: 0.902744163636364

00:15:50.320 --> 00:15:52.308 So here's the assay we did we

NOTE Confidence: 0.902744163636364

00:15:52.308 --> 00:15:54.219 invented and and this is to have

NOTE Confidence: 0.902744163636364

00:15:54.219 --> 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 --> 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 --> 00:16:06.103 make cell lines and with the help of

NOTE Confidence: 0.902744163636364

00:16:06.103 --> 00:16:07.820 array science made a standard curve.

NOTE Confidence: 0.902744163636364

00:16:07.820 --> 00:16:09.948 And then with the help of Crotia we

NOTE Confidence: 0.902744163636364

00:16:09.948 --> 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 --> 00:16:15.639 cell lines and then converted that

NOTE Confidence: 0.902744163636364

00:16:15.639 --> 00:16:17.568 using Q path to how many animals

NOTE Confidence: 0.902744163636364

00:16:17.568 --> 00:16:18.853 per square millimeter there are.

NOTE Confidence: 0.902744163636364

00:16:18.860 --> 00:16:20.540 So now we have an assay.

NOTE Confidence: 0.902744163636364

00:16:20.540 --> 00:16:22.298 That can tell us animals per

NOTE Confidence: 0.902744163636364

00:16:22.298 --> 00:16:22.884 square millimeter.

NOTE Confidence: 0.902744163636364

00:16:22.890 --> 00:16:24.090 And like all assays,

NOTE Confidence: 0.902744163636364

00:16:24.090 --> 00:16:26.250 it saturates when it gets too high.

NOTE Confidence: 0.902744163636364

00:16:26.250 --> 00:16:27.820 So the amplified cases are

NOTE Confidence: 0.902744163636364

00:16:27.820 --> 00:16:29.810 saturated and we can't use those.

NOTE Confidence: 0.902744163636364

00:16:29.810 --> 00:16:30.896 But since we don't really care

NOTE Confidence: 0.902744163636364

00:16:30.896 --> 00:16:32.089 about 2 plus and three plus,

NOTE Confidence: 0.902744163636364

00:16:32.090 --> 00:16:34.290 we got that pathologists can do just fine

NOTE Confidence: 0.902744163636364

00:16:34.290 --> 00:16:36.327 in telling 3 plus from not three plus.

NOTE Confidence: 0.902744163636364

00:16:36.330 --> 00:16:38.625 We need an assay to tell 0 from 1.

NOTE Confidence: 0.902744163636364

00:16:38.630 --> 00:16:40.429 And so that's this assay works fine.

NOTE Confidence: 0.902744163636364

00:16:40.430 --> 00:16:41.725 If we get rid of these two,

NOTE Confidence: 0.902744163636364

00:16:41.730 --> 00:16:43.480 we can now build a very nice

NOTE Confidence: 0.902744163636364

00:16:43.480 --> 00:16:44.974 standard curve that we can use

NOTE Confidence: 0.902744163636364

00:16:44.974 --> 00:16:46.577 as a linear assay and then assign

NOTE Confidence: 0.838703284074074

00:16:46.634 --> 00:16:48.930 each case and animals per square millimeter.

NOTE Confidence: 0.838703284074074

00:16:48.930 --> 00:16:50.550 And so just to remind you.

NOTE Confidence: 0.838703284074074

00:16:50.550 --> 00:16:51.852 I'm going to talk a little bit

NOTE Confidence: 0.838703284074074

00:16:51.852 --> 00:16:52.860 about limits of detection,

NOTE Confidence: 0.838703284074074

00:16:52.860 --> 00:16:53.850 limits of quantification,

NOTE Confidence: 0.838703284074074

00:16:53.850 --> 00:16:55.170 and limits on linearity.

NOTE Confidence: 0.838703284074074

00:16:55.170 --> 00:16:57.290 A little bit of essay terminology and we

NOTE Confidence: 0.838703284074074

00:16:57.290 --> 00:16:59.500 and this is the range we want to be in,

NOTE Confidence: 0.838703284074074

00:16:59.500 --> 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 --> 00:17:04.190 which is what the current

NOTE Confidence: 0.838703284074074

00:17:04.190 --> 00:17:05.636 essay really focuses on.

NOTE Confidence: 0.838703284074074

00:17:05.636 --> 00:17:06.964 Because really the current

NOTE Confidence: 0.838703284074074

00:17:06.964 --> 00:17:08.919 assay all you need to tell is.

NOTE Confidence: 0.838703284074074

00:17:08.920 --> 00:17:10.620 Is it saturated or not?

NOTE Confidence: 0.838703284074074

00:17:10.620 --> 00:17:12.144 For the new assay we need

NOTE Confidence: 0.838703284074074

00:17:12.144 --> 00:17:13.830 to tell how much they have.

NOTE Confidence: 0.838703284074074

00:17:13.830 --> 00:17:17.278 So here's our the current our standard curve.

NOTE Confidence: 0.838703284074074

00:17:17.280 --> 00:17:18.750 With the higher two assay and

NOTE Confidence: 0.838703284074074

00:17:18.750 --> 00:17:20.358 you can see there's two positives

NOTE Confidence: 0.838703284074074

00:17:20.358 --> 00:17:21.788 and the rest are negative.

NOTE Confidence: 0.838703284074074

00:17:21.790 --> 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 --> 00:17:27.300 but what if you want to tell that

NOTE Confidence: 0.838703284074074

00:17:27.300 --> 00:17:28.980 low range so you can see that you

NOTE Confidence: 0.838703284074074

00:17:28.980 --> 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 assay antibody

NOTE Confidence: 0.838703284074074

00:17:32.480 --> 00:17:34.290 concentration or that what we're

NOTE Confidence: 0.838703284074074

00:17:34.290 --> 00:17:36.100 calling high sensitivity HSV or

NOTE Confidence: 0.838703284074074

00:17:36.161 --> 00:17:37.855 two you can see in that range.

NOTE Confidence: 0.838703284074074

00:17:37.860 --> 00:17:39.364 So now we have to talk about a

NOTE Confidence: 0.838703284074074

00:17:39.364 --> 00:17:40.689 little bit of wonky stuff and

NOTE Confidence: 0.838703284074074

00:17:40.689 --> 00:17:42.039 that is what are those things.

NOTE Confidence: 0.838703284074074

00:17:42.040 --> 00:17:43.776 So what is the limit of detection,

NOTE Confidence: 0.838703284074074

00:17:43.780 --> 00:17:45.136 what is the limit of quantification

NOTE Confidence: 0.838703284074074

00:17:45.136 --> 00:17:46.948 or what is the limit of linearity.

NOTE Confidence: 0.838703284074074

00:17:46.950 --> 00:17:47.990 So these are the definitions

NOTE Confidence: 0.838703284074074

00:17:47.990 --> 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 --> 00:17:53.028 advise industry to do this and you

NOTE Confidence: 0.838703284074074

00:17:53.028 --> 00:17:54.915 can see that the limit of detection

NOTE Confidence: 0.838703284074074

00:17:54.915 --> 00:17:56.943 is the lowest concentration of the

NOTE Confidence: 0.838703284074074

00:17:56.943 --> 00:17:58.944 analyte that can be detected but

NOTE Confidence: 0.838703284074074

00:17:58.944 --> 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 --> 00:18:04.698 quantified that is too low.

NOTE Confidence: 0.838703284074074

00:18:04.700 --> 00:18:06.572 So what we really want is to know

NOTE Confidence: 0.838703284074074

00:18:06.572 --> 00:18:07.994 the limit of quantification because

NOTE Confidence: 0.838703284074074

00:18:07.994 --> 00:18:10.420 then we can do it right every time.

NOTE Confidence: 0.838703284074074

00:18:10.420 --> 00:18:12.240 But we don't yet know how much

NOTE Confidence: 0.838703284074074

00:18:12.240 --> 00:18:14.181 her two is required to benefit

NOTE Confidence: 0.838703284074074

00:18:14.181 --> 00:18:16.377 from trust who's mab drug stcan.

NOTE Confidence: 0.838703284074074

00:18:16.380 --> 00:18:17.913 So we're going to measure all the

NOTE Confidence: 0.838703284074074

00:18:17.913 --> 00:18:19.638 way down to beyond the limits of.

NOTE Confidence: 0.838703284074074

00:18:19.640 --> 00:18:22.241 Our essay to to the LD and below and

NOTE Confidence: 0.838703284074074

00:18:22.241 --> 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 --> 00:18:29.587 could see that the the zeros are blue,

NOTE Confidence: 0.838703284074074

00:18:29.590 --> 00:18:31.820 the Reds are one, ones are red, the twos.

NOTE Confidence: 0.838703284074074

00:18:31.820 --> 00:18:33.605 This is the pathologist read over here

NOTE Confidence: 0.838703284074074

00:18:33.605 --> 00:18:35.853 2 Plus is black and three plus is green,

NOTE Confidence: 0.838703284074074

00:18:35.860 --> 00:18:37.240 and most of the Greens are

NOTE Confidence: 0.838703284074074

00:18:37.240 --> 00:18:38.730 above our limit of linearity.

NOTE Confidence: 0.838703284074074

00:18:38.730 --> 00:18:40.794 But look at how many twos and ones

NOTE Confidence: 0.838703284074074

00:18:40.794 --> 00:18:42.607 there are in this middle range.

NOTE Confidence: 0.838703284074074

00:18:42.610 --> 00:18:43.890 That would be called one.

NOTE Confidence: 0.838703284074074

00:18:43.890 --> 00:18:45.850 And I think this is even further evidence

NOTE Confidence: 0.838703284074074

00:18:45.850 --> 00:18:47.790 that we need a a quantitative assay.

NOTE Confidence: 0.838703284074074

00:18:47.790 --> 00:18:49.170 We need a measured assay,

NOTE Confidence: 0.838703284074074

00:18:49.170 --> 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 --> 00:18:51.230 in order to pick the right

NOTE Confidence: 0.838703284074074

00:18:51.279 --> 00:18:52.799 patients for trastuzumab drugs,

NOTE Confidence: 0.838703284074074

00:18:52.800 --> 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 --> 00:18:59.073 but some were called one or two

NOTE Confidence: 0.838703284074074

00:18:59.073 --> 00:19:00.677 that are actually below our limit

NOTE Confidence: 0.838703284074074

00:19:00.677 --> 00:19:02.345 of quantification or even below our

NOTE Confidence: 0.838703284074074

00:19:02.345 --> 00:19:04.237 limit of detection as I'll show later.

NOTE Confidence: 0.838703284074074

00:19:04.240 --> 00:19:06.360 So then we did what you have to do in

NOTE Confidence: 0.808515345625

00:19:06.419 --> 00:19:07.679 a clear lab is did 40,

NOTE Confidence: 0.808515345625

00:19:07.680 --> 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 --> 00:19:14.059 to bring your assay to the CLIA lab.

NOTE Confidence: 0.808515345625

00:19:14.060 --> 00:19:15.887 But we don't have positives and negatives.

NOTE Confidence: 0.808515345625

00:19:15.890 --> 00:19:16.980 We have a continuous scale.

NOTE Confidence: 0.808515345625

00:19:16.980 --> 00:19:18.764 So we did 40 of them and these

NOTE Confidence: 0.808515345625

00:19:18.764 --> 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 --> 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 --> 00:19:26.639 and in fact summarized here,

NOTE Confidence: 0.808515345625

00:19:26.640 --> 00:19:29.656 you can see that there's zeros and ones,

NOTE Confidence: 0.808515345625

00:19:29.660 --> 00:19:32.204 but there's a broad range of animals per

NOTE Confidence: 0.808515345625

00:19:32.204 --> 00:19:33.937 square millimeter for zeros and ones.

NOTE Confidence: 0.808515345625

00:19:33.940 --> 00:19:37.244 And the two plus not amplified almost

NOTE Confidence: 0.808515345625

00:19:37.244 --> 00:19:39.828 in fact does overlap with the two

NOTE Confidence: 0.808515345625

00:19:39.828 --> 00:19:41.580 plus amplifies and the three pluses,

NOTE Confidence: 0.808515345625

00:19:41.580 --> 00:19:44.716 which we're good at and we're pretty tight.

NOTE Confidence: 0.808515345625

00:19:44.720 --> 00:19:45.950 So how many are there?

NOTE Confidence: 0.808515345625

00:19:45.950 --> 00:19:47.942 Well, in our first forty there

NOTE Confidence: 0.808515345625

00:19:47.942 --> 00:19:50.124 was about 20% of the cases that

NOTE Confidence: 0.808515345625

00:19:50.124 --> 00:19:52.378 appear to be below the limit of

NOTE Confidence: 0.808515345625

00:19:52.378 --> 00:19:54.418 quantification for her two protein,

NOTE Confidence: 0.808515345625

00:19:54.420 --> 00:19:57.070 but potentially present and as

NOTE Confidence: 0.808515345625

00:19:57.070 --> 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 --> 00:20:08.701 defined as above the LQ and below the

NOTE Confidence: 0.808515345625

00:20:08.701 --> 00:20:11.000 levels associated with gene amplification.

NOTE Confidence: 0.808515345625

00:20:11.000 --> 00:20:12.908 About 8 to 10% are below

NOTE Confidence: 0.808515345625

00:20:12.908 --> 00:20:14.840 our LQ or even our LD.

NOTE Confidence: 0.808515345625

00:20:14.840 --> 00:20:17.556 It's probably about 6% below our LD.

NOTE Confidence: 0.808515345625

00:20:17.560 --> 00:20:18.600 Many of the cases that

NOTE Confidence: 0.808515345625

00:20:18.600 --> 00:20:19.640 are called her to zero,

NOTE Confidence: 0.808515345625

00:20:19.640 --> 00:20:21.440 as many as 60% are in our studies,

NOTE Confidence: 0.808515345625

00:20:21.440 --> 00:20:23.310 maybe 75% have detectable amounts

NOTE Confidence: 0.808515345625

00:20:23.310 --> 00:20:26.394 of her too between 3 and 20 animals

NOTE Confidence: 0.808515345625

00:20:26.394 --> 00:20:28.680 and the quantitative her two asset

NOTE Confidence: 0.808515345625

00:20:28.680 --> 00:20:31.207 could be envisioned as a reflex tax.

NOTE Confidence: 0.808515345625

00:20:31.210 --> 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 --> 00:20:36.458 they could then reflex to the

NOTE Confidence: 0.808515345625

00:20:36.458 --> 00:20:38.595 quantitative test and the same way we

NOTE Confidence: 0.808515345625

00:20:38.595 --> 00:20:42.620 reflex to fish today for A2 plus HC.

NOTE Confidence: 0.808515345625

00:20:42.620 --> 00:20:45.448 OK, so that's the proposed new assay.

NOTE Confidence: 0.808515345625

00:20:45.450 --> 00:20:46.899 Now let's take it to the clinic.

NOTE Confidence: 0.808515345625

00:20:46.900 --> 00:20:48.406 So what's involved in the next

NOTE Confidence: 0.808515345625

00:20:48.406 --> 00:20:50.040 step of taking to the clinic?

NOTE Confidence: 0.808515345625

00:20:50.040 --> 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 --> 00:20:54.448 who said once you have the essay

NOTE Confidence: 0.808515345625

00:20:54.500 --> 00:20:55.820 working in your research lab,

NOTE Confidence: 0.808515345625

00:20:55.820 --> 00:20:57.770 you're 5% of the way there.

NOTE Confidence: 0.808515345625

00:20:57.770 --> 00:20:59.048 And I think that's really true.

NOTE Confidence: 0.808515345625

00:20:59.050 --> 00:21:00.930 Now having brought this assay

NOTE Confidence: 0.808515345625

00:21:00.930 --> 00:21:03.338 with hats off to Trish Gal who's

NOTE Confidence: 0.808515345625

00:21:03.338 --> 00:21:05.450 not here and has not left,

NOTE Confidence: 0.808515345625

00:21:05.450 --> 00:21:07.997 Nay Chan who was in the audience and Reva

NOTE Confidence: 0.808515345625

00:21:07.997 --> 00:21:10.283 come ova who have helped me to bring

NOTE Confidence: 0.808515345625

00:21:10.283 --> 00:21:12.470 this assay to the clinical setting.

NOTE Confidence: 0.808515345625

00:21:12.470 --> 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 --> 00:21:16.582 maximization of signal to

NOTE Confidence: 0.808515345625

00:21:16.582 --> 00:21:17.806 noise analytic validation.

NOTE Confidence: 0.808515345625

00:21:17.810 --> 00:21:19.482 I'll try to go through this stuff fast

NOTE Confidence: 0.808515345625

00:21:19.482 --> 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 --> 00:21:27.766 And then how do we tell our colleagues?

NOTE Confidence: 0.808515345625

00:21:27.770 --> 00:21:29.180 What do we tell the oncologists?

NOTE Confidence: 0.808515345625

00:21:29.180 --> 00:21:30.584 And then so the reporting is

NOTE Confidence: 0.808515345625

00:21:30.584 --> 00:21:31.840 part of this as well.

NOTE Confidence: 0.808515345625

00:21:31.840 --> 00:21:32.644 So first of all,

NOTE Confidence: 0.808515345625

00:21:32.644 --> 00:21:34.117 we looked at the signal to noise

NOTE Confidence: 0.808515345625

00:21:34.117 --> 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 --> 00:21:40.036 This is a new higher

NOTE Confidence: 0.808515345625

00:21:40.036 --> 00:21:41.400 sensitivity antibody for her

NOTE Confidence: 0.8169936435

00:21:41.463 --> 00:21:42.993 too than the one that's

NOTE Confidence: 0.8169936435

00:21:42.993 --> 00:21:44.523 currently used in the clinic.

NOTE Confidence: 0.8169936435

00:21:44.530 --> 00:21:46.203 And we took and we picked the

NOTE Confidence: 0.8169936435

00:21:46.203 --> 00:21:47.420 concentration with the maximal signal

NOTE Confidence: 0.8169936435

00:21:47.420 --> 00:21:49.220 to noise and then we looked at the

NOTE Confidence: 0.8169936435

00:21:49.271 --> 00:21:51.017 accuracy and our accuracy isn't great,

NOTE Confidence: 0.8169936435

00:21:51.020 --> 00:21:53.666 it's only 87%. Why is that?

NOTE Confidence: 0.8169936435

00:21:53.670 --> 00:21:55.932 That's because we're more sensitive than

NOTE Confidence: 0.8169936435

00:21:55.932 --> 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 --> 00:22:04.565 But overall we have quite a quite

NOTE Confidence: 0.8169936435

00:22:04.565 --> 00:22:06.723 good concordance especially in the end

NOTE Confidence: 0.8169936435

00:22:06.723 --> 00:22:08.984 and more resolution in the low range.

NOTE Confidence: 0.8169936435

00:22:08.990 --> 00:22:11.390 And then our intra and intra

NOTE Confidence: 0.8169936435

00:22:11.390 --> 00:22:13.450 assay precision is quite high,

NOTE Confidence: 0.8169936435

00:22:13.450 --> 00:22:15.178 10% sounds like it might not be great.

NOTE Confidence: 0.8169936435

00:22:15.180 --> 00:22:16.884 To interact assay precision and actually

NOTE Confidence: 0.8169936435

00:22:16.884 --> 00:22:18.858 the essay that we just bridged to,

NOTE Confidence: 0.8169936435

00:22:18.860 --> 00:22:20.308 we're now under 10%,

NOTE Confidence: 0.8169936435

00:22:20.308 --> 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 --> 00:22:25.640 this means to calculate the precision

NOTE Confidence: 0.8169936435

00:22:25.640 --> 00:22:27.363 three slides run on separate

NOTE Confidence: 0.8169936435

00:22:27.363 --> 00:22:29.277 trays at the same machine is,

NOTE Confidence: 0.8169936435

00:22:29.280 --> 00:22:30.392 is, is about 5%.

NOTE Confidence: 0.8169936435

00:22:30.392 --> 00:22:32.519 So these are where we want to be.

NOTE Confidence: 0.8169936435

00:22:32.520 --> 00:22:35.022 Our sensitivity compared to the historical

NOTE Confidence: 0.8169936435

00:22:35.022 --> 00:22:38.520 essay as 100% and our specificity is 84%.

NOTE Confidence: 0.8169936435

00:22:38.520 --> 00:22:39.840 Why is our specificity low?

NOTE Confidence: 0.8169936435

00:22:39.840 --> 00:22:42.025 Because we're more sensitive and

NOTE Confidence: 0.8169936435

00:22:42.025 --> 00:22:44.721 so we call cases positive that

NOTE Confidence: 0.8169936435

00:22:44.721 --> 00:22:46.856 we're called negative by IHC.

NOTE Confidence: 0.8169936435

00:22:46.860 --> 00:22:48.770 So here's the proposed clinical

NOTE Confidence: 0.8169936435

00:22:48.770 --> 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 --> 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 --> 00:22:58.481 quantitative diagnostics and anatomic

NOTE Confidence: 0.8169936435

00:22:58.481 --> 00:23:00.283 pathology which is a new lab which

NOTE Confidence: 0.8169936435

00:23:00.283 --> 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 --> 00:23:06.500 This is and this is qdap essay #1,

NOTE Confidence: 0.8169936435

00:23:06.500 --> 00:23:07.956 the high sensitivity here.

NOTE Confidence: 0.8169936435

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

NOTE Confidence: 0.8169936435

00:23:08.320 --> 00:23:09.881 we batched the stains and do them

NOTE Confidence: 0.8169936435

00:23:09.881 --> 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 --> 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 --> 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 --> 00:23:26.046 he will see it shortly and uses a

NOTE Confidence: 0.8169936435

00:23:26.046 --> 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 --> 00:23:31.590 take about four minutes to scan a slide.

NOTE Confidence: 0.8169936435

00:23:31.590 --> 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 --> 00:23:37.450 it out and Co path as a procedure.

NOTE Confidence: 0.8169936435

00:23:37.450 --> 00:23:39.284 And so it ultimately makes it to

NOTE Confidence: 0.8169936435

00:23:39.284 --> 00:23:41.409 epic and and clinicians can see it,

NOTE Confidence: 0.8169936435

00:23:41.410 --> 00:23:42.790 this is what it looks like.

NOTE Confidence: 0.8169936435

00:23:42.790 --> 00:23:44.288 The pathologist has to pick a region.

NOTE Confidence: 0.8169936435

00:23:44.290 --> 00:23:45.890 So we're actually not measuring

NOTE Confidence: 0.8169936435

00:23:45.890 --> 00:23:47.170 the entire core biopsy.

NOTE Confidence: 0.8169936435

00:23:47.170 --> 00:23:49.114 We're measuring a region that is

NOTE Confidence: 0.8169936435

00:23:49.114 --> 00:23:50.783 quote UN quote representative and

NOTE Confidence: 0.8169936435

00:23:50.783 --> 00:23:52.059 that representative region is

NOTE Confidence: 0.8169936435

00:23:52.059 --> 00:23:53.335 then looks like this.

NOTE Confidence: 0.8169936435

00:23:53.340 --> 00:23:54.999 This is actually not a brown stain

NOTE Confidence: 0.8169936435

00:23:54.999 --> 00:23:57.074 but a pseudo IHC which it shows the

NOTE Confidence: 0.8169936435

00:23:57.074 --> 00:23:58.748 pathologist what they what it looked

NOTE Confidence: 0.8169936435

00:23:58.748 --> 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 --> 00:24:06.003 in this case 23 and the in this case

NOTE Confidence: 0.8169936435

00:24:06.003 --> 00:24:08.860 the rare sight score in this case was

NOTE Confidence: 0.8169936435

00:24:08.860 --> 00:24:10.540 15.4 animals per square millimeter.

NOTE Confidence: 0.8169936435

00:24:10.540 --> 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 --> 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 --> 00:24:19.052 we do know that it's detectable

NOTE Confidence: 0.8169936435

00:24:19.052 --> 00:24:19.520 and then

NOTE Confidence: 0.830076910416667

00:24:19.570 --> 00:24:21.594 we can give a choice in our interpretation

NOTE Confidence: 0.830076910416667

00:24:21.594 --> 00:24:23.567 that it's positive for expression high.

NOTE Confidence: 0.830076910416667

00:24:23.570 --> 00:24:26.266 That is, it's above our limit of linearity

NOTE Confidence: 0.830076910416667

00:24:26.266 --> 00:24:27.710 positive expression intermediate,

NOTE Confidence: 0.830076910416667

00:24:27.710 --> 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 --> 00:24:33.284 which means it's.

NOTE Confidence: 0.830076910416667

00:24:33.284 --> 00:24:36.700 Present, but it might not be reproducible.

NOTE Confidence: 0.830076910416667

00:24:36.700 --> 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 --> 00:24:42.646 and then negative below the LOD.

NOTE Confidence: 0.830076910416667

00:24:42.650 --> 00:24:45.210 And so these are the reports that we'll

NOTE Confidence: 0.830076910416667

00:24:45.210 --> 00:24:48.115 issue as as we start to receive specimens.

NOTE Confidence: 0.830076910416667

00:24:48.120 --> 00:24:51.234 So far we've received a grand total of two.

NOTE Confidence: 0.830076910416667

00:24:51.240 --> 00:24:53.632 We hope that after this talk and maybe

NOTE Confidence: 0.830076910416667

00:24:53.632 --> 00:24:56.501 in the future and certainly in the more

NOTE Confidence: 0.830076910416667

00:24:56.501 --> 00:24:58.970 distant future when we know how much.

NOTE Confidence: 0.830076910416667

00:24:58.970 --> 00:25:01.550 Is necessary for patients to respond.

NOTE Confidence: 0.830076910416667

00:25:01.550 --> 00:25:03.386 We hope that this essay will

NOTE Confidence: 0.830076910416667

00:25:03.386 --> 00:25:04.304 gain some traction.

NOTE Confidence: 0.830076910416667

00:25:04.310 --> 00:25:07.424 So our vision we currently offer HSR 2 in

NOTE Confidence: 0.830076910416667

00:25:07.424 --> 00:25:09.952 the QDAP lab test must be requested by an

NOTE Confidence: 0.830076910416667

00:25:09.952 --> 00:25:11.469 oncologist and the patients are billed.

NOTE Confidence: 0.830076910416667

00:25:11.470 --> 00:25:13.790 If the test is requested by an oncologist,

NOTE Confidence: 0.830076910416667

00:25:13.790 --> 00:25:16.254 there are I CD9 codes for all

NOTE Confidence: 0.830076910416667

00:25:16.254 --> 00:25:17.860 the stuff we're doing.

NOTE Confidence: 0.830076910416667

00:25:17.860 --> 00:25:20.436 We began a prospective study on all

NOTE Confidence: 0.830076910416667

00:25:20.436 --> 00:25:23.317 breast biopsies so that we have data of

NOTE Confidence: 0.830076910416667

00:25:23.317 --> 00:25:25.788 a year's worth of prospective data and

NOTE Confidence: 0.830076910416667

00:25:25.788 --> 00:25:28.224 we're about seven months into it now.

NOTE Confidence: 0.830076910416667

00:25:28.230 --> 00:25:29.915 We offer the essay coalitions

NOTE Confidence: 0.830076910416667

00:25:29.915 --> 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 --> 00:25:35.580 but only two so far to date.

NOTE Confidence: 0.830076910416667

00:25:35.580 --> 00:25:37.500 And then the discussions of the

NOTE Confidence: 0.830076910416667

00:25:37.500 --> 00:25:38.460 license we will.

NOTE Confidence: 0.830076910416667

00:25:38.460 --> 00:25:40.042 What we hope to happen is ultimately

NOTE Confidence: 0.830076910416667

00:25:40.042 --> 00:25:41.896 it won't just be yell that can do this,

NOTE Confidence: 0.830076910416667

00:25:41.900 --> 00:25:43.377 but we'll license it to some of

NOTE Confidence: 0.830076910416667

00:25:43.377 --> 00:25:44.915 the big lab companies that provide

NOTE Confidence: 0.830076910416667

00:25:44.915 --> 00:25:46.619 them the bulk of the service.

NOTE Confidence: 0.830076910416667

00:25:46.620 --> 00:25:48.005 It's interesting to know and

NOTE Confidence: 0.830076910416667

00:25:48.005 --> 00:25:49.113 interesting to me anyway,

NOTE Confidence: 0.830076910416667

00:25:49.120 --> 00:25:51.640 that only 15% of lab tests in the

NOTE Confidence: 0.830076910416667

00:25:51.640 --> 00:25:54.399 US are provided by academic labs.

NOTE Confidence: 0.830076910416667

00:25:54.400 --> 00:25:57.736 The other 85% are provided by private labs.

NOTE Confidence: 0.830076910416667

00:25:57.740 --> 00:25:59.000 And so clearly if we want to.

NOTE Confidence: 0.830076910416667

00:25:59.000 --> 00:26:02.378 Have this effect patients around

NOTE Confidence: 0.830076910416667

00:26:02.378 --> 00:26:04.646 the world and be useful and needs

NOTE Confidence: 0.830076910416667

00:26:04.646 --> 00:26:07.361 to make it into private labs and

NOTE Confidence: 0.830076910416667

00:26:07.361 --> 00:26:08.909 those discussions are beginning.

NOTE Confidence: 0.830076910416667

00:26:08.910 --> 00:26:11.770 So the last thing I want to talk about is

NOTE Confidence: 0.830076910416667

00:26:11.770 --> 00:26:14.650 the precision versus persuasion medicine.

NOTE Confidence: 0.830076910416667

00:26:14.650 --> 00:26:16.900 And so our original envision for

NOTE Confidence: 0.830076910416667

00:26:16.900 --> 00:26:19.590 this essay was that we would need

NOTE Confidence: 0.830076910416667

00:26:19.590 --> 00:26:21.412 to adjudicate the IHC's equal 0.

NOTE Confidence: 0.830076910416667

00:26:21.412 --> 00:26:23.628 And what we would do is we would get

NOTE Confidence: 0.830076910416667

00:26:23.628 --> 00:26:25.684 all the HC equals zero and we would

NOTE Confidence: 0.830076910416667

00:26:25.746 --> 00:26:27.986 measure them and then we tell you if

NOTE Confidence: 0.830076910416667

00:26:27.986 --> 00:26:29.590 you're above the limit of detection

NOTE Confidence: 0.830076910416667

00:26:29.590 --> 00:26:31.150 or above the limit of response.

NOTE Confidence: 0.830076910416667

00:26:31.150 --> 00:26:33.126 We don't know the limit of response yet.

NOTE Confidence: 0.830076910416667

00:26:33.130 --> 00:26:34.887 Someday we will and I'll show you

NOTE Confidence: 0.830076910416667

00:26:34.887 --> 00:26:36.388 how we intend to get there.

NOTE Confidence: 0.830076910416667

00:26:36.390 --> 00:26:37.692 But right now we don't know the

NOTE Confidence: 0.830076910416667

00:26:37.692 --> 00:26:38.440 limit of response but.

NOTE Confidence: 0.830076910416667

00:26:38.440 --> 00:26:40.421 You would take all the cases that

NOTE Confidence: 0.830076910416667

00:26:40.421 --> 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 --> 00:26:46.256 But something happened in the last

NOTE Confidence: 0.830076910416667

00:26:46.256 --> 00:26:48.170 three or four months and I haven't

NOTE Confidence: 0.830076910416667

00:26:48.170 --> 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 --> 00:26:55.370 but suddenly the IHC equals zero is rare.

NOTE Confidence: 0.830076910416667

00:26:55.370 --> 00:26:57.150 And that's because pathologists

NOTE Confidence: 0.830076910416667

00:26:57.150 --> 00:26:58.485 are people too.

NOTE Confidence: 0.830076910416667

00:26:58.490 --> 00:26:59.878 Pathologists sometimes might be

NOTE Confidence: 0.830076910416667

00:26:59.878 --> 00:27:01.960 a little more lenient on what

NOTE Confidence: 0.795286742857143

00:27:02.026 --> 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 --> 00:27:07.329 then they can get this new drug.

NOTE Confidence: 0.795286742857143

00:27:07.330 --> 00:27:09.087 Here are real quotes that I've heard.

NOTE Confidence: 0.795286742857143

00:27:09.090 --> 00:27:11.736 I won't quote the people because to

NOTE Confidence: 0.795286742857143

00:27:11.736 --> 00:27:14.347 not embarrass them or give them credit,

NOTE Confidence: 0.795286742857143

00:27:14.350 --> 00:27:15.540 but here's a real quote.

NOTE Confidence: 0.795286742857143

00:27:15.540 --> 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 --> 00:27:20.716 That means I'm going to have

NOTE Confidence: 0.795286742857143

00:27:20.716 --> 00:27:22.120 to offer her brain radiation.

NOTE Confidence: 0.795286742857143

00:27:22.120 --> 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 --> 00:27:32.086 Does that mean that my first view

NOTE Confidence: 0.86010612

00:27:32.086 --> 00:27:34.060 of that slide was not accurate?

NOTE Confidence: 0.86010612

00:27:34.060 --> 00:27:36.316 Or was it accurate and maybe

NOTE Confidence: 0.86010612

00:27:36.316 --> 00:27:38.700 I should change my diagnosis?

NOTE Confidence: 0.86010612

00:27:38.700 --> 00:27:40.652 Because I'm persuaded that

NOTE Confidence: 0.86010612

00:27:40.652 --> 00:27:43.092 that's better for the patient.

NOTE Confidence: 0.86010612

00:27:43.100 --> 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 --> 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 --> 00:27:53.152 I'm not seeing the response rates

NOTE Confidence: 0.86010612

00:27:53.152 --> 00:27:54.744 and in her two patients that

NOTE Confidence: 0.86010612

00:27:54.744 --> 00:27:56.448 they saw in the clinical trial.

NOTE Confidence: 0.86010612

00:27:56.450 --> 00:27:59.221 They're getting a lot of IHC zeros and

NOTE Confidence: 0.86010612

00:27:59.221 --> 00:28:01.087 maybe IHC zeros really don't respond.

NOTE Confidence: 0.86010612

00:28:01.090 --> 00:28:03.570 We know that eight to 10% of the

NOTE Confidence: 0.86010612

00:28:03.570 --> 00:28:05.670 cases really don't express any target

NOTE Confidence: 0.86010612

00:28:05.670 --> 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 --> 00:28:10.430 know how the drug works,

NOTE Confidence: 0.86010612

00:28:10.430 --> 00:28:12.509 but we think it's a targeted therapy.

NOTE Confidence: 0.86010612

00:28:12.510 --> 00:28:13.572 After all,

NOTE Confidence: 0.86010612

00:28:13.572 --> 00:28:16.227 it's trastuzumab conjugated to toxins.

NOTE Confidence: 0.86010612

00:28:16.230 --> 00:28:18.120 So what's happened is that really

NOTE Confidence: 0.86010612

00:28:18.120 --> 00:28:20.568 now we need to adjudicate the one

NOTE Confidence: 0.86010612

00:28:20.568 --> 00:28:22.812 pluses what we really need because

NOTE Confidence: 0.86010612

00:28:22.812 --> 00:28:24.885 the zeros have minimized, not,

NOTE Confidence: 0.86010612

00:28:24.885 --> 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 --> 00:28:32.066 of course we still call IHC 0.

NOTE Confidence: 0.86010612

00:28:32.070 --> 00:28:33.610 But.

NOTE Confidence: 0.86010612

00:28:33.610 --> 00:28:35.773 Data will set will will tell us

NOTE Confidence: 0.86010612

00:28:35.773 --> 00:28:38.493 in a year or so from now how

NOTE Confidence: 0.86010612

00:28:38.493 --> 00:28:39.865 our IC0 calls changed.

NOTE Confidence: 0.86010612

00:28:39.870 --> 00:28:41.949 But but I see one is now more common

NOTE Confidence: 0.86010612

00:28:41.949 --> 00:28:44.138 and so if it's if it's more common

NOTE Confidence: 0.86010612

00:28:44.138 --> 00:28:46.149 maybe that's the one we should be

NOTE Confidence: 0.86010612

00:28:46.149 --> 00:28:48.202 measuring and in fact that's the plan.

NOTE Confidence: 0.86010612

00:28:48.202 --> 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 --> 00:28:58.280 prospective study and this is

NOTE Confidence: 0.86010612

00:28:58.280 --> 00:29:00.616 copied with me by name by Nate Chan,

NOTE Confidence: 0.86010612

00:29:00.620 --> 00:29:02.540 who's the director of the Q dot lab.

NOTE Confidence: 0.86010612

00:29:02.540 --> 00:29:04.878 And you can see we began August

NOTE Confidence: 0.86010612

00:29:04.878 --> 00:29:07.312 1 and we'll go till July 2023

NOTE Confidence: 0.86010612

00:29:07.312 --> 00:29:09.325 and today we have 226.

NOTE Confidence: 0.86010612

00:29:09.325 --> 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 --> 00:29:15.293 case and the primary objective will

NOTE Confidence: 0.86010612

00:29:15.293 --> 00:29:17.693 be to determine the number of H0 cases

NOTE Confidence: 0.86010612

00:29:17.753 --> 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 --> 00:29:22.815 And this study was designed

NOTE Confidence: 0.86010612

00:29:22.815 --> 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 --> 00:29:26.200 but how many HC Zeros have above

NOTE Confidence: 0.86010612

00:29:26.267 --> 00:29:28.395 the limit of detection and how many

NOTE Confidence: 0.86010612

00:29:28.395 --> 00:29:30.819 HC ones have below the limit of

NOTE Confidence: 0.86010612

00:29:30.819 --> 00:29:32.985 detection will be interesting as well.

NOTE Confidence: 0.86010612

00:29:32.990 --> 00:29:34.109 That's a secondary,

NOTE Confidence: 0.86010612

00:29:34.109 --> 00:29:36.347 that's a secondary objective of the

NOTE Confidence: 0.86010612

00:29:36.347 --> 00:29:38.362 study and the study is in process

NOTE Confidence: 0.86010612

00:29:38.362 --> 00:29:40.637 and we all just to show you a peak,

NOTE Confidence: 0.86010612

00:29:40.640 --> 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 --> 00:29:48.220 this is quantification of prospective

NOTE Confidence: 0.86010612

00:29:48.220 --> 00:29:50.145 tissue from the clinical trial

NOTE Confidence: 0.86010612

00:29:50.145 --> 00:29:53.009 and you can see the lol in this

NOTE Confidence: 0.86010612

00:29:53.009 --> 00:29:55.240 case was 33 and the OD is 3.

NOTE Confidence: 0.86010612

00:29:55.240 --> 00:29:57.000 This is all done on the new platform

NOTE Confidence: 0.86010612

00:29:57.000 --> 00:29:58.820 and you can see that there's a lot

NOTE Confidence: 0.86010612

00:29:58.820 --> 00:30:00.611 of cases that are called zeros that

NOTE Confidence: 0.86010612

00:30:00.611 --> 00:30:02.315 are above our limit of detection.

NOTE Confidence: 0.86010612

00:30:02.320 --> 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 --> 00:30:09.540 but time will tell as we get

NOTE Confidence: 0.86010612

00:30:09.540 --> 00:30:10.320 as the study

NOTE Confidence: 0.833837779090909

00:30:10.391 --> 00:30:12.580 matures. There's two other studies

NOTE Confidence: 0.833837779090909

00:30:12.580 --> 00:30:15.546 that were progressing on one is a

NOTE Confidence: 0.833837779090909

00:30:15.546 --> 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 --> 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 --> 00:30:26.456 which is a group of 16 or 17.

NOTE Confidence: 0.833837779090909

00:30:26.460 --> 00:30:28.590 Now institutions that do studies

NOTE Confidence: 0.833837779090909

00:30:28.590 --> 00:30:30.294 together on translational research

NOTE Confidence: 0.833837779090909

00:30:30.294 --> 00:30:32.512 and the goal of this study that

NOTE Confidence: 0.833837779090909

00:30:32.512 --> 00:30:34.645 is still in proposal stage is to

NOTE Confidence: 0.833837779090909

00:30:34.645 --> 00:30:36.175 evaluate her two measurement in

NOTE Confidence: 0.833837779090909

00:30:36.175 --> 00:30:37.762 the one plus metastatic cases.

NOTE Confidence: 0.833837779090909

00:30:37.762 --> 00:30:41.314 So if we get one pluses and we get 2 or

NOTE Confidence: 0.833837779090909

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

NOTE Confidence: 0.833837779090909

00:30:43.730 --> 00:30:46.334 we should be able to tell how

NOTE Confidence: 0.833837779090909

00:30:46.334 --> 00:30:48.120 frequently we see the patients

NOTE Confidence: 0.833837779090909

00:30:48.120 --> 00:30:50.130 that have one plus actually don't

NOTE Confidence: 0.833837779090909

00:30:50.130 --> 00:30:52.207 have any target and vice versa,

NOTE Confidence: 0.833837779090909

00:30:52.210 --> 00:30:53.666 we should be able to see response

NOTE Confidence: 0.833837779090909

00:30:53.666 --> 00:30:55.016 since all those patients since they

NOTE Confidence: 0.833837779090909

00:30:55.016 --> 00:30:56.591 were called one plus will be get.

NOTE Confidence: 0.833837779090909

00:30:56.600 --> 00:30:58.217 Drug will be getting trustors map drugs

NOTE Confidence: 0.833837779090909

00:30:58.217 --> 00:31:00.246 he can and be present in the residency.

NOTE Confidence: 0.833837779090909

00:31:00.250 --> 00:31:02.610 So here's the study a draft of the

NOTE Confidence: 0.833837779090909

00:31:02.610 --> 00:31:04.441 study objectives to evaluate the

NOTE Confidence: 0.833837779090909

00:31:04.441 --> 00:31:06.013 real world relationship between

NOTE Confidence: 0.833837779090909

00:31:06.013 --> 00:31:07.977 quantitative her two expression QIF

NOTE Confidence: 0.833837779090909

00:31:07.977 --> 00:31:09.772 and objective response in patients

NOTE Confidence: 0.833837779090909

00:31:09.772 --> 00:31:12.522 with her two IHC plus one and

NOTE Confidence: 0.833837779090909

00:31:12.522 --> 00:31:14.612 metastatic breast cancer receiving TXT.

NOTE Confidence: 0.833837779090909

00:31:14.620 --> 00:31:17.077 And then there's a number of secondary

NOTE Confidence: 0.833837779090909

00:31:17.077 --> 00:31:19.338 objectives that are shown here as well.

NOTE Confidence: 0.833837779090909

00:31:19.340 --> 00:31:21.174 And then a second study that I,

NOTE Confidence: 0.833837779090909

00:31:21.180 --> 00:31:23.524 I don't even have a slide for yet

NOTE Confidence: 0.833837779090909

00:31:23.524 --> 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 --> 00:31:31.396 who get HC0 and then prospectively

NOTE Confidence: 0.833837779090909

00:31:31.396 --> 00:31:34.982 giving them TXD much the way the

NOTE Confidence: 0.833837779090909

00:31:34.982 --> 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 --> 00:31:42.078 and not yet completely approved.

NOTE Confidence: 0.833837779090909

00:31:42.080 --> 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 --> 00:31:48.430 we need where we have patient response.

NOTE Confidence: 0.833837779090909

00:31:48.430 --> 00:31:50.230 Either real-world patient response or

NOTE Confidence: 0.833837779090909

00:31:50.230 --> 00:31:52.375 clinical trial patient response in order

NOTE Confidence: 0.833837779090909

00:31:52.375 --> 00:31:54.440 to figure out the animals per square

NOTE Confidence: 0.833837779090909

00:31:54.440 --> 00:31:56.229 millimeter above which patients benefit.

NOTE Confidence: 0.833837779090909

00:31:56.230 --> 00:31:57.490 Will it be a cut point?

NOTE Confidence: 0.833837779090909

00:31:57.490 --> 00:31:58.100 Probably not.

NOTE Confidence: 0.833837779090909

00:31:58.100 --> 00:31:59.930 Probably there will be patients with

NOTE Confidence: 0.833837779090909

00:31:59.930 --> 00:32:01.528 high animals per square millimeter

NOTE Confidence: 0.833837779090909

00:32:01.528 --> 00:32:03.388 that still don't benefit because there

NOTE Confidence: 0.833837779090909

00:32:03.388 --> 00:32:05.259 are other mechanisms of resistance.

NOTE Confidence: 0.833837779090909

00:32:05.260 --> 00:32:07.268 And I have and one of the interesting

NOTE Confidence: 0.833837779090909

00:32:07.268 --> 00:32:08.853 topics that many labs are working

NOTE Confidence: 0.833837779090909

00:32:08.853 --> 00:32:10.752 on including my own are what are

NOTE Confidence: 0.833837779090909

00:32:10.752 --> 00:32:12.267 the mechanisms of resistance beyond

NOTE Confidence: 0.833837779090909

00:32:12.267 --> 00:32:14.024 just not enough her to present.

NOTE Confidence: 0.833837779090909

00:32:14.024 --> 00:32:15.928 And hopefully next year or a couple

NOTE Confidence: 0.833837779090909

00:32:15.928 --> 00:32:18.146 years from now I'll come back to you at

NOTE Confidence: 0.833837779090909

00:32:18.146 --> 00:32:19.868 grand Rounds and talk about mechanisms

NOTE Confidence: 0.833837779090909

00:32:19.868 --> 00:32:22.082 of resistance and a more complex assay

NOTE Confidence: 0.833837779090909

00:32:22.082 --> 00:32:25.036 that also doesn't just assay her too,

NOTE Confidence: 0.833837779090909

00:32:25.040 --> 00:32:26.900 but maybe assays other biomarkers

NOTE Confidence: 0.833837779090909

00:32:26.900 --> 00:32:28.760 that are associated with resistance.

NOTE Confidence: 0.833837779090909

00:32:28.760 --> 00:32:29.546 Or other drugs.

NOTE Confidence: 0.833837779090909

00:32:29.546 --> 00:32:31.380 And in fact the her two trope

NOTE Confidence: 0.833837779090909

00:32:31.441 --> 00:32:33.184 2 assay as well along its way.

NOTE Confidence: 0.833837779090909

00:32:33.190 --> 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 --> 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 --> 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,

NOTE Confidence: 0.833837779090909

00:32:47.160 --> 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 --> 00:32:53.468 you probably don't do them here

NOTE Confidence: 0.833837779090909

00:32:53.468 --> 00:32:55.416 since most of our assays are LDT's,

NOTE Confidence: 0.833837779090909

00:32:55.416 --> 00:32:58.440 but we do have a few FDA approved assays

NOTE Confidence: 0.811140847333333

00:32:58.521 --> 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 --> 00:33:03.758 committees you realize this,

NOTE Confidence: 0.811140847333333

00:33:03.760 --> 00:33:05.769 if you change one step of the

NOTE Confidence: 0.811140847333333

00:33:05.769 --> 00:33:07.879 protocol of your FDA approved assay,

NOTE Confidence: 0.811140847333333

00:33:07.880 --> 00:33:10.634 it is then an LDT and you must thus

NOTE Confidence: 0.811140847333333

00:33:10.634 --> 00:33:12.540 validate it and so most assays.

NOTE Confidence: 0.811140847333333

00:33:12.540 --> 00:33:14.670 We do are not FDA approved.

NOTE Confidence: 0.811140847333333

00:33:14.670 --> 00:33:16.710 We might use FDA approved reagents,

NOTE Confidence: 0.811140847333333

00:33:16.710 --> 00:33:19.480 but most assays we do are actually LDT's in

NOTE Confidence: 0.811140847333333

00:33:19.480 --> 00:33:21.970 our lab and in all the labs around the world.

NOTE Confidence: 0.811140847333333

00:33:21.970 --> 00:33:25.646 And that also applies for molecular assays,

NOTE Confidence: 0.811140847333333

00:33:25.646 --> 00:33:27.350 gene mutation assays.

NOTE Confidence: 0.811140847333333

00:33:27.350 --> 00:33:29.394 Many of those assays are also not

NOTE Confidence: 0.811140847333333

00:33:29.394 --> 00:33:32.280 FDA approved assays but rather LDT's.

NOTE Confidence: 0.811140847333333

00:33:32.280 --> 00:33:34.827 HSR 2 essay is in the correct dynamic range.

NOTE Confidence: 0.811140847333333

00:33:34.830 --> 00:33:37.126 That is, we're not weighing elephants on or

NOTE Confidence: 0.811140847333333

00:33:37.126 --> 00:33:39.316 weighing mice on a scale built for elephants.

NOTE Confidence: 0.811140847333333

00:33:39.320 --> 00:33:41.175 The level of target required for trustees,

NOTE Confidence: 0.811140847333333

00:33:41.180 --> 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 --> 00:33:46.378 want to try to hide that from you.

NOTE Confidence: 0.811140847333333

00:33:46.380 --> 00:33:48.156 I think it's very clear that we don't

NOTE Confidence: 0.811140847333333

00:33:48.156 --> 00:33:49.999 know the answer to this question yet.

NOTE Confidence: 0.811140847333333

00:33:50.000 --> 00:33:51.960 But if we waited until we knew the answer to

NOTE Confidence: 0.811140847333333

00:33:52.009 --> 00:33:53.836 the question before we started the essay,

NOTE Confidence: 0.811140847333333

00:33:53.840 --> 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 --> 00:33:59.988 for a couple years now to get it

NOTE Confidence: 0.811140847333333

00:33:59.988 --> 00:34:01.332 to the point that it's at.

NOTE Confidence: 0.811140847333333

00:34:01.340 --> 00:34:02.558 And so now that we have.

NOTE Confidence: 0.811140847333333

00:34:02.560 --> 00:34:04.807 Tools, I am asked that oncologists in

NOTE Confidence: 0.811140847333333

00:34:04.807 --> 00:34:06.839 the audience ask for measurements,

NOTE Confidence: 0.811140847333333

00:34:06.840 --> 00:34:07.944 not for readings.

NOTE Confidence: 0.811140847333333

00:34:07.944 --> 00:34:10.152 And please don't ask the pathologist

NOTE Confidence: 0.811140847333333

00:34:10.152 --> 00:34:11.818 to change their minds.

NOTE Confidence: 0.811140847333333

00:34:11.820 --> 00:34:13.260 That's persuasion Madison,

NOTE Confidence: 0.811140847333333

00:34:13.260 --> 00:34:14.700 not precision medicine.

NOTE Confidence: 0.811140847333333

00:34:14.700 --> 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,

NOTE Confidence: 0.811140847333333

00:34:18.632 --> 00:34:20.704 I know that oncologists really think highly

NOTE Confidence: 0.811140847333333

00:34:20.704 --> 00:34:23.174 of most of the pathologists they work with.

NOTE Confidence: 0.811140847333333

00:34:23.180 --> 00:34:25.294 And I think that they don't realize

NOTE Confidence: 0.811140847333333

00:34:25.294 --> 00:34:27.503 that when they do pursue persuasion

NOTE Confidence: 0.811140847333333

00:34:27.503 --> 00:34:29.445 medicine that it's actually not

NOTE Confidence: 0.811140847333333

00:34:29.445 --> 00:34:31.155 what the biologist wants to hear.

NOTE Confidence: 0.811140847333333

00:34:31.160 --> 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 --> 00:34:38.920 we really believe that's right.

NOTE Confidence: 0.811140847333333

00:34:38.920 --> 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 --> 00:34:44.868 It's if.

NOTE Confidence: 0.811140847333333

00:34:44.870 --> 00:34:46.190 If that was your first impression,

NOTE Confidence: 0.811140847333333

00:34:46.190 --> 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 --> 00:34:50.950 And so with that,

NOTE Confidence: 0.811140847333333

00:34:50.950 --> 00:34:52.051 I just want to thank the people

NOTE Confidence: 0.811140847333333

00:34:52.051 --> 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 --> 00:34:56.171 but it's really a crew of people that do

NOTE Confidence: 0.811140847333333

00:34:56.171 --> 00:34:58.004 all this stuff that I told you about.

NOTE Confidence: 0.811140847333333

00:34:58.010 --> 00:35:00.103 I especially like to point out mirror

NOTE Confidence: 0.811140847333333

00:35:00.103 --> 00:35:02.357 to Matafi who started that and started

NOTE Confidence: 0.811140847333333

00:35:02.357 --> 00:35:04.667 building this essay in the lab over

NOTE Confidence: 0.811140847333333

00:35:04.667 --> 00:35:07.155 two years ago now and then my Yale

NOTE Confidence: 0.811140847333333

00:35:07.155 --> 00:35:09.054 collaborators and funding sources etcetera.

NOTE Confidence: 0.811140847333333

00:35:09.054 --> 00:35:11.862 And then here's the 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 --> 00:35:17.506 She was involved in a lot

NOTE Confidence: 0.811140847333333

00:35:17.506 --> 00:35:18.530 of the analytic stuff.

NOTE Confidence: 0.811140847333333

00:35:18.530 --> 00:35:20.474 Matt Lou helped out with some of the.

NOTE Confidence: 0.811140847333333

00:35:20.480 --> 00:35:21.988 Analytic stuff as well.

NOTE Confidence: 0.811140847333333

00:35:21.988 --> 00:35:24.108 And then and Jack and Katie

NOTE Confidence: 0.811140847333333

00:35:24.108 --> 00:35:25.020 weren't at the party,

NOTE Confidence: 0.811140847333333

00:35:25.020 --> 00:35:26.820 so they got their picture separate.

NOTE Confidence: 0.797865172727273

00:35:26.820 --> 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 --> 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 --> 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 --> 00:35:45.270 should I start with those?

NOTE Confidence: 0.86163855125

00:35:45.270 --> 00:35:46.450 Oh no, there's only two.

NOTE Confidence: 0.86163855125

00:35:46.450 --> 00:35:47.958 What about discordance with

NOTE Confidence: 0.86163855125

00:35:47.958 --> 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 --> 00:35:57.792 asks a very pivotal question, that is.

NOTE Confidence: 0.86163855125

00:35:57.792 --> 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 --> 00:36:01.830 when you read it once,

NOTE Confidence: 0.86163855125

00:36:01.830 --> 00:36:02.817 if you're going to read it again,

NOTE Confidence: 0.86163855125

00:36:02.820 --> 00:36:04.200 you should have a washout period.

NOTE Confidence: 0.86163855125

00:36:04.200 --> 00:36:05.928 That is so you don't remember

NOTE Confidence: 0.86163855125

00:36:05.928 --> 00:36:07.080 that case because surprisingly,

NOTE Confidence: 0.86163855125

00:36:07.080 --> 00:36:09.110 pathologists have a really good memory for

NOTE Confidence: 0.86163855125

00:36:09.110 --> 00:36:10.918 what the morphology of cases look like,

NOTE Confidence: 0.86163855125

00:36:10.920 --> 00:36:12.714 and they can also remember the

NOTE Confidence: 0.86163855125

00:36:12.714 --> 00:36:14.320 patient's name on the label.

NOTE Confidence: 0.86163855125

00:36:14.320 --> 00:36:16.322 And so a lot of studies have

NOTE Confidence: 0.86163855125

00:36:16.322 --> 00:36:17.180 a washout period.

NOTE Confidence: 0.86163855125

00:36:17.180 --> 00:36:19.196 We didn't need a washout period in this

NOTE Confidence: 0.86163855125

00:36:19.196 --> 00:36:21.179 study because they only saw the slides once.

NOTE Confidence: 0.86163855125

00:36:21.180 --> 00:36:23.241 So if we're going to show them to them

NOTE Confidence: 0.86163855125

00:36:23.241 --> 00:36:25.063 again and if we're going to do any

NOTE Confidence: 0.86163855125

00:36:25.063 --> 00:36:27.079 kind of intra observer reproducibility,

NOTE Confidence: 0.86163855125

00:36:27.080 --> 00:36:28.532 which we didn't do and some

NOTE Confidence: 0.86163855125

00:36:28.532 --> 00:36:29.500 other studies have done,

NOTE Confidence: 0.86163855125

00:36:29.500 --> 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 --> 00:36:33.820 a washout period was not required.

NOTE Confidence: 0.86163855125

00:36:33.820 --> 00:36:36.620 And then Timothy Robinson asks,

NOTE Confidence: 0.86163855125

00:36:36.620 --> 00:36:37.715 is heterogeneity within

NOTE Confidence: 0.86163855125

00:36:37.715 --> 00:36:39.175 the tumor important issue?

NOTE Confidence: 0.86163855125

00:36:39.180 --> 00:36:40.716 Is it more important to do a small

NOTE Confidence: 0.86163855125

00:36:40.716 --> 00:36:41.791 percentage of cancer cells that

NOTE Confidence: 0.86163855125

00:36:41.791 --> 00:36:43.291 express a high amount of heart, too?

NOTE Confidence: 0.86163855125

00:36:43.291 --> 00:36:44.819 Or is it more important to know that

NOTE Confidence: 0.86163855125

00:36:44.819 --> 00:36:46.609 a high number of cells expressed at

NOTE Confidence: 0.86163855125

00:36:46.609 --> 00:36:48.179 least the minimum amount of her too?

NOTE Confidence: 0.86163855125

00:36:48.180 --> 00:36:49.530 Wow, phenomenal question.

NOTE Confidence: 0.86163855125

00:36:49.530 --> 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 --> 00:36:53.860 I think that's a great question.

NOTE Confidence: 0.86163855125

00:36:53.860 --> 00:36:55.636 We obviously don't know the answer.

NOTE Confidence: 0.86163855125

00:36:55.640 --> 00:36:57.200 All the pathologists in the audience

NOTE Confidence: 0.86163855125

00:36:57.200 --> 00:36:59.359 know that her two is very heterogeneous.

NOTE Confidence: 0.86163855125

00:36:59.360 --> 00:37:01.245 Not only is it heterogeneous

NOTE Confidence: 0.86163855125

00:37:01.245 --> 00:37:02.753 from within a slide,

NOTE Confidence: 0.86163855125

00:37:02.760 --> 00:37:04.720 but it's heterogeneous between cuts.

NOTE Confidence: 0.86163855125

00:37:04.720 --> 00:37:06.400 And all the pathologists in the audience

NOTE Confidence: 0.86163855125

00:37:06.400 --> 00:37:08.037 know that when we sample one core

NOTE Confidence: 0.86163855125

00:37:08.037 --> 00:37:09.841 biopsy that's less than 1% of the tumor.

NOTE Confidence: 0.86163855125

00:37:09.841 --> 00:37:12.282 And so there's no way for us to actually

NOTE Confidence: 0.86163855125

00:37:12.282 --> 00:37:14.087 answer that question about true

NOTE Confidence: 0.86163855125

00:37:14.087 --> 00:37:16.080 heterogeneity of the patients tumor.

NOTE Confidence: 0.86163855125

00:37:16.080 --> 00:37:16.980 But what we can add,

NOTE Confidence: 0.86163855125

00:37:16.980 --> 00:37:18.345 we can ask about heterogeneity

NOTE Confidence: 0.86163855125

00:37:18.345 --> 00:37:20.613 on the slide and we can and are

NOTE Confidence: 0.86163855125

00:37:20.613 --> 00:37:21.737 asking at that question.

NOTE Confidence: 0.86163855125

00:37:21.740 --> 00:37:22.344 That is,

NOTE Confidence: 0.86163855125

00:37:22.344 --> 00:37:23.854 how important is high expression

NOTE Confidence: 0.86163855125

00:37:23.854 --> 00:37:25.855 in a single cell versus high

NOTE Confidence: 0.86163855125

00:37:25.855 --> 00:37:27.570 expression in the average cell?

NOTE Confidence: 0.86163855125

00:37:27.570 --> 00:37:28.610 We started with the average.

NOTE Confidence: 0.86163855125

00:37:28.610 --> 00:37:30.110 You have to start somewhere,

NOTE Confidence: 0.86163855125

00:37:30.110 --> 00:37:31.454 and I don't know that the

NOTE Confidence: 0.86163855125

00:37:31.454 --> 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 --> 00:37:35.943 the bystander effect of TDXD,

NOTE Confidence: 0.86163855125

00:37:35.943 --> 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 --> 00:37:41.370 but we don't know that.

NOTE Confidence: 0.86163855125

00:37:41.370 --> 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 --> 00:37:50.810 It doesn't.

NOTE Confidence: 0.86163855125

00:37:50.810 --> 00:37:51.240 Say.

NOTE Confidence: 0.87842585

00:37:54.980 --> 00:37:56.140 That's a great question.

NOTE Confidence: 0.798758137692308

00:37:59.010 --> 00:37:59.882 We can do more.

NOTE Confidence: 0.798758137692308

00:37:59.882 --> 00:38:02.249 So as soon as I had the assay built,

NOTE Confidence: 0.798758137692308

00:38:02.250 --> 00:38:04.902 I applied for tissue from AstraZeneca

NOTE Confidence: 0.798758137692308

00:38:04.902 --> 00:38:07.867 adicci senko from the Destiny 4 trial

NOTE Confidence: 0.798758137692308

00:38:07.867 --> 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 --> 00:38:16.414 They have their own people that

NOTE Confidence: 0.798758137692308

00:38:16.414 --> 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 --> 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 --> 00:38:25.712 They're making a lot of money on this

NOTE Confidence: 0.798758137692308

00:38:25.712 --> 00:38:27.647 drug and it would be detrimental to

NOTE Confidence: 0.798758137692308

00:38:27.647 --> 00:38:29.368 the shareholders of that company to

NOTE Confidence: 0.798758137692308

00:38:29.368 --> 00:38:30.985 have me have access to that tissue.

NOTE Confidence: 0.9305174

00:38:33.870 --> 00:38:36.688 My question was how much heterogeneity

NOTE Confidence: 0.9305174

00:38:36.690 --> 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 --> 00:38:46.430 a lot of heterogeneity there or is it?

NOTE Confidence: 0.9305174

00:38:46.430 --> 00:38:49.230 So that's a great question.

NOTE Confidence: 0.9305174

00:38:49.230 --> 00:38:51.062 Heterogeneity within a core

NOTE Confidence: 0.9305174

00:38:51.062 --> 00:38:52.894 biopsy is quite substantial.

NOTE Confidence: 0.9305174

00:38:52.900 --> 00:38:54.756 And as you know when you read them,

NOTE Confidence: 0.9305174

00:38:54.760 --> 00:38:57.316 you see bright areas and not so bright areas.

NOTE Confidence: 0.9305174

00:38:57.320 --> 00:38:59.360 And you know how do we handle that?

NOTE Confidence: 0.9305174

00:38:59.360 --> 00:39:01.220 Well, someday we'll know how you

NOTE Confidence: 0.9305174

00:39:01.220 --> 00:39:03.423 know whether it's the highest sell or

NOTE Confidence: 0.9305174

00:39:03.423 --> 00:39:05.516 the average sell or the lowest sell.

NOTE Confidence: 0.9305174

00:39:05.520 --> 00:39:07.200 That's most important for response

NOTE Confidence: 0.9305174

00:39:07.200 --> 00:39:08.544 to Trump drug seeking.

NOTE Confidence: 0.9305174

00:39:08.550 --> 00:39:10.056 But we don't know that yet.

NOTE Confidence: 0.9305174

00:39:10.060 --> 00:39:12.644 And so in the same vein of OK,

NOTE Confidence: 0.9305174

00:39:12.650 --> 00:39:14.855 we're just going to take a core biopsy and

NOTE Confidence: 0.9305174

00:39:14.855 --> 00:39:17.125 say that that represents the whole tumor,

NOTE Confidence: 0.9305174

00:39:17.130 --> 00:39:18.324 we're going to just take the

NOTE Confidence: 0.9305174

00:39:18.324 --> 00:39:19.370 average and say that that.

NOTE Confidence: 0.9305174

00:39:19.370 --> 00:39:22.136 Represents the expression of her too.

NOTE Confidence: 0.9305174

00:39:22.140 --> 00:39:22.990 And the second question

NOTE Confidence: 0.9305174

00:39:22.990 --> 00:39:24.615 moved for the clinician.

NOTE Confidence: 0.9305174

00:39:24.615 --> 00:39:27.430 We see situations with heterogeneity

NOTE Confidence: 0.9305174

00:39:27.430 --> 00:39:30.522 where we have a clear 3 plus tumor where

NOTE Confidence: 0.9305174

00:39:30.522 --> 00:39:32.928 the patient gets you know trastuzumab

NOTE Confidence: 0.9305174

00:39:32.928 --> 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 --> 00:39:41.942 know one plus which didn't respond.

NOTE Confidence: 0.9305174

00:39:41.942 --> 00:39:44.828 So what will these patients benefit

NOTE Confidence: 0.9305174

00:39:44.828 --> 00:39:48.120 from a second round of DXD or

NOTE Confidence: 0.9305174

00:39:48.120 --> 00:39:51.630 when they have two distinct?

NOTE Confidence: 0.9305174

00:39:51.630 --> 00:39:54.780 Her two profiles to maybe I can use the

NOTE Confidence: 0.9305174

00:39:54.780 --> 00:39:57.370 microphone since there's 71 people online.

NOTE Confidence: 0.71368902

00:39:58.240 --> 00:39:59.934 Yeah, when I but I, I do want

NOTE Confidence: 0.71368902

00:39:59.934 --> 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 --> 00:40:06.895 We wouldn't have used a standard her

NOTE Confidence: 0.837351195714286

00:40:06.895 --> 00:40:09.077 two therapy if they were one plus.

NOTE Confidence: 0.6665299375

00:40:13.180 --> 00:40:13.940 Why don't we choose?

NOTE Confidence: 0.8049838

00:40:18.090 --> 00:40:22.410 Do we use her two therapy, I mean. Yeah.

NOTE Confidence: 0.832513583333333

00:40:24.600 --> 00:40:25.428 But the patient?

NOTE Confidence: 0.5355477925

00:40:29.210 --> 00:40:30.598 Patient had complete response

NOTE Confidence: 0.69599822

00:40:30.610 --> 00:40:33.874 to that through. So it was our CB0,

NOTE Confidence: 0.69599822

00:40:33.880 --> 00:40:36.364 but then the tumor which was

NOTE Confidence: 0.69599822

00:40:36.364 --> 00:40:38.020 one plus still extensive.

NOTE Confidence: 0.881571676

00:40:39.340 --> 00:40:41.044 Yeah so I mean it depends

NOTE Confidence: 0.881571676

00:40:41.044 --> 00:40:42.180 on the clinical situation.

NOTE Confidence: 0.881571676

00:40:42.180 --> 00:40:44.616 We know pretty clearly now that with

NOTE Confidence: 0.881571676

00:40:44.620 --> 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 therapies that

NOTE Confidence: 0.881571676

00:40:48.826 --> 00:40:51.017 you do not see any benefit with non

NOTE Confidence: 0.881571676

00:40:51.017 --> 00:40:53.519 her 2/3 plus or amplified cancer.

NOTE Confidence: 0.881571676

00:40:53.520 --> 00:40:55.000 So the her two lows do not respond

NOTE Confidence: 0.881571676

00:40:55.000 --> 00:40:56.801 to the previous generation any of the

NOTE Confidence: 0.881571676

00:40:56.801 --> 00:40:58.680 previous generation of her two therapies.

NOTE Confidence: 0.881571676

00:40:58.680 --> 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 --> 00:41:08.014 you might you would see potentially

NOTE Confidence: 0.881571676

00:41:08.014 --> 00:41:09.299 could see benefit both.

NOTE Confidence: 0.881571676

00:41:09.300 --> 00:41:10.890 And that clearly amplified in

NOTE Confidence: 0.881571676

00:41:10.890 --> 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 --> 00:41:20.262 the her two therapy to get rid of

NOTE Confidence: 0.881571676

00:41:20.262 --> 00:41:21.822 that usually more aggressive her

NOTE Confidence: 0.881571676

00:41:21.822 --> 00:41:23.726 two her two positive cancer and

NOTE Confidence: 0.881571676

00:41:23.726 --> 00:41:25.826 then we'll worry about the her two

NOTE Confidence: 0.881571676

00:41:25.826 --> 00:41:27.750 negative or her two low cancer later.

NOTE Confidence: 0.881571676

00:41:27.750 --> 00:41:29.556 But it's it's you know again the

NOTE Confidence: 0.881571676

00:41:29.556 --> 00:41:31.625 the field is evolving now that we

NOTE Confidence: 0.881571676

00:41:31.625 --> 00:41:33.479 have these drugs that work across

NOTE Confidence: 0.881571676

00:41:33.544 --> 00:41:35.149 different levels of her too.

NOTE Confidence: 0.881571676

00:41:35.150 --> 00:41:36.958 I mean getting to in your earlier point

NOTE Confidence: 0.881571676

00:41:36.958 --> 00:41:38.606 that the two questions were brought

NOTE Confidence: 0.881571676

00:41:38.606 --> 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 --> 00:41:43.520 Again with the first generation,

NOTE Confidence: 0.881571676

00:41:43.520 --> 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 --> 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 --> 00:41:55.680 that doesn't have bystander effect

NOTE Confidence: 0.881571676

00:41:55.748 --> 00:41:58.172 and in that study a heterogeneous

NOTE Confidence: 0.881571676

00:41:58.172 --> 00:42:00.530 cancer responded much work much less.

NOTE Confidence: 0.881571676

00:42:00.530 --> 00:42:02.315 Effectively to a heterogeneous cancer

NOTE Confidence: 0.881571676

00:42:02.315 --> 00:42:05.016 than it did to a non heterogeneous

NOTE Confidence: 0.881571676

00:42:05.016 --> 00:42:07.131 cancer and and quantitatively that

NOTE Confidence: 0.881571676

00:42:07.131 --> 00:42:09.621 the to your specific question what

NOTE Confidence: 0.881571676

00:42:09.621 --> 00:42:12.302 mattered was the percent of her two

NOTE Confidence: 0.881571676

00:42:12.310 --> 00:42:14.575 negative cells not the intensity

NOTE Confidence: 0.881571676

00:42:14.575 --> 00:42:18.120 of her two on themselves.

NOTE Confidence: 0.881571676

00:42:18.120 --> 00:42:20.507 Again with a drug that has bystander

NOTE Confidence: 0.881571676

00:42:20.507 --> 00:42:23.281 effect as as I think David was alluding

NOTE Confidence: 0.881571676

00:42:23.281 --> 00:42:25.144 to that might be switched and maybe

NOTE Confidence: 0.881571676

00:42:25.144 --> 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 --> 00:42:30.585 positive cells to get the drug in.

NOTE Confidence: 0.881571676

00:42:30.590 --> 00:42:32.182 And then the and then the bystander effect

NOTE Confidence: 0.881571676

00:42:32.182 --> 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 --> 00:42:37.908 prospectively with we haven't.

NOTE Confidence: 0.881571676

00:42:37.910 --> 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 --> 00:42:49.727 Is any do you have any information?

NOTE Confidence: 0.886226237142857

00:42:49.730 --> 00:42:53.588 The conjugate drug can get activated.

NOTE Confidence: 0.886226237142857

00:42:53.590 --> 00:42:55.880 In the extracellular and

NOTE Confidence: 0.886226237142857

00:42:55.880 --> 00:42:57.774 microenvironment of tumor cells.

NOTE Confidence: 0.886226237142857

00:42:57.774 --> 00:43:01.110 So I I would again defer to Ian,

NOTE Confidence: 0.886226237142857

00:43:01.110 --> 00:43:01.940 who's much more of an

NOTE Confidence: 0.886226237142857

00:43:01.940 --> 00:43:02.930 expert on this than I am.

NOTE Confidence: 0.886226237142857

00:43:02.930 --> 00:43:05.324 But it's my understanding that the drug,

NOTE Confidence: 0.886226237142857

00:43:05.330 --> 00:43:06.466 once it comes off,

NOTE Confidence: 0.886226237142857

00:43:06.466 --> 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 --> 00:43:12.550 it survives in the extracellular environment.

NOTE Confidence: 0.886226237142857

00:43:12.550 --> 00:43:14.419 And that's how the bystander effect works.

NOTE Confidence: 0.886226237142857

00:43:14.420 --> 00:43:16.408 That's how it can kill neighboring cells.

NOTE Confidence: 0.886226237142857

00:43:16.410 --> 00:43:20.100 Bystander effect doesn't really require.

NOTE Confidence: 0.886226237142857

00:43:20.100 --> 00:43:25.430 To go into the cells as long as it's a.

NOTE Confidence: 0.886226237142857

00:43:25.430 --> 00:43:28.320 Present in the microenvironment of the

NOTE Confidence: 0.886226237142857

00:43:28.320 --> 00:43:30.750 tumor cell in the enriched fashion

NOTE Confidence: 0.886226237142857

00:43:30.750 --> 00:43:32.649 you you will have some activities.

NOTE Confidence: 0.886226237142857

00:43:32.649 --> 00:43:34.767 Well the drug is an inhibitor

NOTE Confidence: 0.886226237142857

00:43:34.767 --> 00:43:36.110 of topoisomerase,

NOTE Confidence: 0.886226237142857

00:43:36.110 --> 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 --> 00:43:41.630 you can get activate.

NOTE Confidence: 0.886226237142857

00:43:41.630 --> 00:43:42.260 Outside

NOTE Confidence: 0.930902697142857

00:43:42.270 --> 00:43:45.180 of the cells. You don't have to take

NOTE Confidence: 0.930902697142857

00:43:45.180 --> 00:43:47.280 anybody to go inside the cells.

NOTE Confidence: 0.786440327826087

00:43:48.130 --> 00:43:50.176 Right, but that that that but

NOTE Confidence: 0.786440327826087

00:43:50.176 --> 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 --> 00:43:55.229 into cells without the antibody,

NOTE Confidence: 0.786440327826087

00:43:55.230 --> 00:43:57.474 but the reason they conjugated to

NOTE Confidence: 0.786440327826087

00:43:57.474 --> 00:43:59.416 antibodies so you can increase

NOTE Confidence: 0.786440327826087

00:43:59.416 --> 00:44:01.684 the dose locally to the tumor.

NOTE Confidence: 0.786440327826087

00:44:01.690 --> 00:44:02.920 Michael environment.

NOTE Confidence: 0.786440327826087

00:44:02.920 --> 00:44:07.240 We have a more protease type.

NOTE Confidence: 0.786440327826087

00:44:07.240 --> 00:44:10.648 To break up the linkage between

NOTE Confidence: 0.786440327826087

00:44:10.648 --> 00:44:13.192 conjugate drug and the conjugate ohh,

NOTE Confidence: 0.786440327826087

00:44:13.192 --> 00:44:14.668 that'd be fine.

NOTE Confidence: 0.786440327826087

00:44:14.668 --> 00:44:18.353 That that that means you read that

NOTE Confidence: 0.786440327826087

00:44:18.353 --> 00:44:22.656 could partly explain why the the

NOTE Confidence: 0.786440327826087

00:44:22.656 --> 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 --> 00:44:31.250 have another interesting parameter

NOTE Confidence: 0.786440327826087

00:44:31.250 --> 00:44:35.938 to assess now today with the.

NOTE Confidence: 0.786440327826087

00:44:35.940 --> 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 --> 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 --> 00:44:46.452 And in that case you would

NOTE Confidence: 0.786440327826087

00:44:46.452 --> 00:44:47.760 argue that it worked.

NOTE Confidence: 0.786440327826087

00:44:47.760 --> 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 --> 00:44:52.522 You could you get the deconjugation

NOTE Confidence: 0.786440327826087

00:44:52.522 --> 00:44:54.739 even if there's no target present.

NOTE Confidence: 0.786440327826087

00:44:54.740 --> 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 --> 00:45:01.641 present if if the if if it's a true her

NOTE Confidence: 0.786440327826087

00:45:01.641 --> 00:45:03.869 20 the drug could still work because

NOTE Confidence: 0.786440327826087

00:45:03.869 --> 00:45:06.730 it could get deconjugation and be effective.

NOTE Confidence: 0.786440327826087

00:45:06.730 --> 00:45:09.410 Everywhere in the body.

NOTE Confidence: 0.786440327826087

00:45:09.410 --> 00:45:12.300 Anywhere in the exercise room.

NOTE Confidence: 0.786440327826087

00:45:12.300 --> 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 --> 00:45:18.282 the the question is the toxicity

NOTE Confidence: 0.786440327826087

00:45:18.282 --> 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 --> 00:45:22.451 But one of the problems with this

NOTE Confidence: 0.786440327826087

00:45:22.451 --> 00:45:24.237 drug is it has pulmonary toxicity

NOTE Confidence: 0.786440327826087

00:45:24.237 --> 00:45:26.012 and that patients get interstitial

NOTE Confidence: 0.786440327826087

00:45:26.012 --> 00:45:27.938 lung disease about 10% of the time.

NOTE Confidence: 0.786440327826087

00:45:27.938 --> 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 --> 00:45:33.308 And one wonders if perhaps the

NOTE Confidence: 0.786440327826087

00:45:33.308 --> 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 --> 00:45:38.920 extracellular environment cleaving the

NOTE Confidence: 0.786440327826087

00:45:38.920 --> 00:45:42.288 drug even in the absence of her too,

NOTE Confidence: 0.786440327826087

00:45:42.290 --> 00:45:43.410 although we've also found

NOTE Confidence: 0.786440327826087

00:45:43.410 --> 00:45:44.810 that her two is present.

NOTE Confidence: 0.786440327826087

00:45:44.810 --> 00:45:47.366 Normal Airways at about the level it is in,

NOTE Confidence: 0.786440327826087

00:45:47.370 --> 00:45:49.379 low in low in about at about

NOTE Confidence: 0.786440327826087

00:45:49.379 --> 00:45:51.370 1/4 UN quote one plus level,

NOTE Confidence: 0.786440327826087

00:45:51.370 --> 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.