WEBVTT

NOTE duration:"01:02:08"

NOTE recognizability:0.878

NOTE language:en-us

NOTE Confidence: 0.809758734444444

00:00:00.000 --> 00:00:01.881 OK, let's begin.

NOTE Confidence: 0.809758734444444

00:00:01.881 --> 00:00:03.762 Welcome everybody to

NOTE Confidence: 0.809758734444444

00:00:03.762 --> 00:00:06.001 pathology grand rounds today.

NOTE Confidence: 0.809758734444444

00:00:06.001 --> 00:00:08.107 I'm excited to introduce our speaker,

NOTE Confidence: 0.809758734444444

00:00:08.110 --> 00:00:09.870 Christina Curtis from Stanford.

NOTE Confidence: 0.809758734444444

00:00:09.870 --> 00:00:11.630 Christina comes has quite

NOTE Confidence: 0.809758734444444

00:00:11.630 --> 00:00:13.749 a long training history.

NOTE Confidence: 0.809758734444444

00:00:13.750 --> 00:00:15.514 Beginning in Heidel, Heidelberg,

NOTE Confidence: 0.809758734444444

00:00:15.514 --> 00:00:18.160 Germany for a Masters degree and

NOTE Confidence: 0.809758734444444

00:00:18.228 --> 00:00:20.668 then did her doctorate at USC and in

NOTE Confidence: 0.809758734444444

00:00:20.670 --> 00:00:23.300 computational and Molecular Biology program.

NOTE Confidence: 0.809758734444444

00:00:23.300 --> 00:00:24.615 Did a postdoc back over

NOTE Confidence: 0.809758734444444

00:00:24.615 --> 00:00:25.930 across the ocean in Cambridge,

NOTE Confidence: 0.809758734444444

00:00:25.930 --> 00:00:28.128 then came back to USC to begin

NOTE Confidence: 0.809758734444444

00:00:28.128 --> 00:00:29.830 as an assistant professor,

NOTE Confidence: 0.809758734444444

00:00:29.830 --> 00:00:31.048 but shortly thereafter.

NOTE Confidence: 0.809758734444444

00:00:31.048 --> 00:00:33.078 Joined Stanford as an assistant

NOTE Confidence: 0.809758734444444

00:00:33.078 --> 00:00:35.548 professor there and is now at the

NOTE Confidence: 0.809758734444444

00:00:35.548 --> 00:00:37.148 associate professor level at Stanford,

NOTE Confidence: 0.809758734444444

00:00:37.150 --> 00:00:39.450 and as you can see.

NOTE Confidence: 0.809758734444444

00:00:39.450 --> 00:00:40.593 We in pathology.

NOTE Confidence: 0.809758734444444

00:00:40.593 --> 00:00:43.260 Most of the people are in pathology,

NOTE Confidence: 0.809758734444444

00:00:43.260 --> 00:00:44.836 grand rounds or some way related to that.

NOTE Confidence: 0.809758734444444

00:00:44.840 --> 00:00:46.835 I've had a long appreciation for the

NOTE Confidence: 0.809758734444444

00:00:46.835 --> 00:00:48.330 importance of spatial information,

NOTE Confidence: 0.809758734444444

00:00:48.330 --> 00:00:50.652 but many of our genomics colleagues

NOTE Confidence: 0.809758734444444

00:00:50.652 --> 00:00:53.101 just grounded all up and I think

NOTE Confidence: 0.809758734444444

00:00:53.101 --> 00:00:55.084 that one of the reasons I was

NOTE Confidence: 0.809758734444444

00:00:55.084 --> 00:00:56.220 excited to invite Christina.

NOTE Confidence: 0.809758734444444

00:00:56.220 --> 00:00:57.672 She's one of those people that

NOTE Confidence: 0.809758734444444

00:00:57.672 --> 00:00:59.720 not only is an expert in genomics,

NOTE Confidence: 0.809758734444444

00:00:59.720 --> 00:01:00.596 as you can see,

NOTE Confidence: 0.809758734444444

00:01:00.596 --> 00:01:01.910 she's the director of the breast

NOTE Confidence: 0.809758734444444

00:01:01.965 --> 00:01:03.669 Cancer Translational unit and the Co

NOTE Confidence: 0.809758734444444

00:01:03.669 --> 00:01:05.400 director of the Molecular Tumor Board.

NOTE Confidence: 0.809758734444444

00:01:05.400 --> 00:01:07.130 But she's also very conscious,

NOTE Confidence: 0.809758734444444

00:01:07.130 --> 00:01:08.806 conscious of spatial information.

NOTE Confidence: 0.809758734444444

00:01:08.806 --> 00:01:11.812 And so the mixing of genomic information

NOTE Confidence: 0.809758734444444

00:01:11.812 --> 00:01:15.172 and spatial information is not an easy task,

NOTE Confidence: 0.809758734444444

00:01:15.180 --> 00:01:17.696 but I think Christina Curtis is

NOTE Confidence: 0.809758734444444

00:01:17.696 --> 00:01:19.208 one of the world leaders on this,

NOTE Confidence: 0.809758734444444

00:01:19.210 --> 00:01:21.360 even though she's still fairly

NOTE Confidence: 0.809758734444444

00:01:21.360 --> 00:01:23.038 junior and so rather than go through

NOTE Confidence: 0.809758734444444

00:01:23.038 --> 00:01:24.242 all the awards and fellowships

NOTE Confidence: 0.809758734444444

00:01:24.242 --> 00:01:25.867 and leadership positions she had,

NOTE Confidence: 0.809758734444444

00:01:25.870 --> 00:01:27.678 I'm going to let her speak for herself.

NOTE Confidence: 0.809758734444444

00:01:27.680 --> 00:01:29.448 And she's going to tell us about toward

NOTE Confidence: 0.809758734444444

00:01:29.448 --> 00:01:30.550 predictive markers and early stage.

NOTE Confidence: 0.809758734444444

00:01:30.550 --> 00:01:32.720 Her two positive breast cancer, Christina.

NOTE Confidence: 0.91529736

00:01:33.650 --> 00:01:35.336 Great, thanks so much for the

NOTE Confidence: 0.91529736

00:01:35.336 --> 00:01:36.800 kind introduction, David and I,

NOTE Confidence: 0.91529736

00:01:36.800 --> 00:01:39.230 I am delighted to share this with you.

NOTE Confidence: 0.91529736

00:01:39.230 --> 00:01:42.198 I hope next time. To be in person,

NOTE Confidence: 0.91529736

00:01:42.200 --> 00:01:45.370 as I'm sure we all do but but yeah,

NOTE Confidence: 0.91529736

00:01:45.370 --> 00:01:46.410 really delighted to share

NOTE Confidence: 0.91529736

00:01:46.410 --> 00:01:47.740 this sort of recent work,

NOTE Confidence: 0.91529736

00:01:47.740 --> 00:01:50.036 and I think often I have to say

NOTE Confidence: 0.91529736

00:01:50.036 --> 00:01:51.947 I've drawn a lot of inspiration

NOTE Confidence: 0.91529736

00:01:51.947 --> 00:01:54.250 from from you David in in this,

NOTE Confidence: 0.91529736

00:01:54.250 --> 00:01:55.295 as you were obviously a

NOTE Confidence: 0.91529736

00:01:55.295 --> 00:01:56.340 pioneer early in the field,

NOTE Confidence: 0.91529736

00:01:56.340 --> 00:01:58.174 and so we've been sort of waiting

NOTE Confidence: 0.91529736

00:01:58.174 --> 00:01:59.501 for these technologies to make

NOTE Confidence: 0.91529736

00:01:59.501 --> 00:02:02.020 it to a place where where they

NOTE Confidence: 0.91529736

00:02:02.020 --> 00:02:03.550 can be utilized by the masses,

NOTE Confidence: 0.91529736

00:02:03.550 --> 00:02:05.485 and so that that's what I'll speak to today.

NOTE Confidence: 0.91529736

00:02:05.490 --> 00:02:07.709 I'll just state these are my disclosures.

NOTE Confidence: 0.91529736

00:02:07.710 --> 00:02:09.782 The only point that is relevant to

NOTE Confidence: 0.91529736

00:02:09.782 --> 00:02:11.536 the discussion today is that I am a.

NOTE Confidence: 0.91529736

00:02:11.540 --> 00:02:12.440 Scientific advisor,

NOTE Confidence: 0.91529736

00:02:12.440 --> 00:02:15.590 banana string and I will discuss the

NOTE Confidence: 0.91529736

00:02:15.590 --> 00:02:17.419 mastering DSP technology and work

NOTE Confidence: 0.91529736

00:02:17.419 --> 00:02:20.000 that I had done Prior to joining.

NOTE Confidence: 0.91529736

00:02:20.000 --> 00:02:21.520 So as we all know,

NOTE Confidence: 0.91529736

00:02:21.520 --> 00:02:25.804 I'm a major objective of our current

NOTE Confidence: 0.91529736

00:02:25.804 --> 00:02:29.110 times is to affect precision oncology,

NOTE Confidence: 0.91529736

00:02:29.110 --> 00:02:32.540 and there's many pieces to this puzzle

NOTE Confidence: 0.91529736

00:02:32.624 --> 00:02:35.039 that range from really improving

NOTE Confidence: 0.91529736

00:02:35.040 --> 00:02:36.992 our understanding of prognostication

NOTE Confidence: 0.91529736

00:02:36.992 --> 00:02:38.456 through biomarker discovery,

NOTE Confidence: 0.91529736

00:02:38.460 --> 00:02:40.777 as well as predicting response to therapy,

NOTE Confidence: 0.91529736

00:02:40.780 --> 00:02:42.064 improving patient stratification,

NOTE Confidence: 0.91529736

00:02:42.064 --> 00:02:42.920 and ultimately,

NOTE Confidence: 0.91529736

00:02:42.920 --> 00:02:45.727 this goes on and actually can inform

NOTE Confidence: 0.91529736

00:02:45.727 --> 00:02:47.640 the drug development pipeline.

NOTE Confidence: 0.91529736

00:02:47.640 --> 00:02:50.048 And so there's a number of key goals.

NOTE Confidence: 0.91529736

00:02:50.050 --> 00:02:50.392 Here,

NOTE Confidence: 0.91529736

00:02:50.392 --> 00:02:53.470 mainly what I will focus on as a key

NOTE Confidence: 0.91529736

00:02:53.552 --> 00:02:56.448 area of interest from my own group is

NOTE Confidence: 0.91529736

00:02:56.448 --> 00:02:59.098 on patient stratification and really

NOTE Confidence: 0.91529736

00:02:59.098 --> 00:03:01.386 identifying aggressive subgroups of

NOTE Confidence: 0.91529736

00:03:01.386 --> 00:03:04.328 disease and tailoring our therapeutic

NOTE Confidence: 0.91529736

00:03:04.328 --> 00:03:06.628 approaches for these subgroups.

NOTE Confidence: 0.91529736

00:03:06.630 --> 00:03:08.070 Another key objective and and

NOTE Confidence: 0.91529736

00:03:08.070 --> 00:03:10.029 I will touch on this as well,

NOTE Confidence: 0.91529736

00:03:10.030 --> 00:03:11.914 is really on being able to

NOTE Confidence: 0.91529736

00:03:11.914 --> 00:03:13.170 predict response to therapy.

NOTE Confidence: 0.91529736

00:03:13.170 --> 00:03:15.123 And of course this is not only

NOTE Confidence: 0.91529736

00:03:15.123 --> 00:03:17.127 our new targeted and immunotherapy

NOTE Confidence: 0.91529736

00:03:17.127 --> 00:03:18.227 therapeutic agents,

NOTE Confidence: 0.91529736

00:03:18.230 --> 00:03:19.784 but also chemotherapeutic.

NOTE Confidence: 0.91529736

00:03:19.784 --> 00:03:22.892 Back bones that really remain the

NOTE Confidence: 0.91529736

00:03:22.892 --> 00:03:24.892 mainstay of many treatment regimes,

NOTE Confidence: 0.91529736

00:03:24.892 --> 00:03:26.636 but have been hard.

NOTE Confidence: 0.91529736

00:03:26.640 --> 00:03:28.754 A hard nut to crack with respect

NOTE Confidence: 0.91529736

00:03:28.754 --> 00:03:30.466 to prediction of response and

NOTE Confidence: 0.91529736

00:03:30.466 --> 00:03:32.434 ultimately a lot of the work in my

NOTE Confidence: 0.91529736

00:03:32.434 --> 00:03:34.615 own lab and I I won't dwell on this.

NOTE Confidence: 0.91529736

00:03:34.620 --> 00:03:36.475 I'll focus more on sort of the

NOTE Confidence: 0.91529736

00:03:36.475 --> 00:03:37.632 applications of these approaches

NOTE Confidence: 0.91529736

00:03:37.632 --> 00:03:39.774 is has been to use systems biology

NOTE Confidence: 0.91529736

00:03:39.774 --> 00:03:41.420 techniques and and I would say

NOTE Confidence: 0.91529736

00:03:41.420 --> 00:03:43.185 that one of the potential powers of

NOTE Confidence: 0.91529736

00:03:43.185 --> 00:03:45.250 this type of approach is that we're

NOTE Confidence: 0.91529736

00:03:45.250 --> 00:03:47.466 not only interested in developing

NOTE Confidence: 0.91529736

00:03:47.466 --> 00:03:49.546 predictive models or classifiers,

NOTE Confidence: 0.91529736

00:03:49.550 --> 00:03:51.380 but actually unraveling the biology

NOTE Confidence: 0.91529736

00:03:51.380 --> 00:03:52.844 so that we can.

NOTE Confidence: 0.91529736

00:03:52.850 --> 00:03:56.130 And develop mechanistic insights

NOTE Confidence: 0.91529736

00:03:56.130 --> 00:03:57.898 into into disease,

NOTE Confidence: 0.91529736

00:03:57.898 --> 00:04:01.216 and perhaps inform the next wave of

NOTE Confidence: 0.91529736

00:04:01.216 --> 00:04:03.427 therapeutic approaches and so really,

NOTE Confidence: 0.91529736

00:04:03.427 --> 00:04:05.716 what I'll talk about today is sort

NOTE Confidence: 0.91529736

00:04:05.716 --> 00:04:08.685 of a few pieces from my own labs work

NOTE Confidence: 0.91529736

00:04:08.685 --> 00:04:11.808 that have led from really omic technologies,

NOTE Confidence: 0.91529736

00:04:11.810 --> 00:04:13.935 but that are now moving

NOTE Confidence: 0.91529736

00:04:13.935 --> 00:04:15.210 towards clinical translation.

NOTE Confidence: 0.91529736

00:04:15.210 --> 00:04:17.667 Of course, across a very long road,

NOTE Confidence: 0.91529736

00:04:17.670 --> 00:04:19.680 and so the first story that

NOTE Confidence: 0.91529736

00:04:19.680 --> 00:04:22.139 I'll talk about really is about

NOTE Confidence: 0.91529736

00:04:22.139 --> 00:04:23.708 leveraging spatial approaches.

NOTE Confidence: 0.91529736

00:04:23.710 --> 00:04:25.400 In situ proteomic profiling to

NOTE Confidence: 0.91529736

00:04:25.400 --> 00:04:27.090 predict response in this case

NOTE Confidence: 0.91529736

00:04:27.152 --> 00:04:28.976 to her two targeted agents and

NOTE Confidence: 0.91529736

00:04:28.976 --> 00:04:30.650 her two positive breast cancer,

NOTE Confidence: 0.91529736

00:04:30.650 --> 00:04:32.275 and I'll describe really how

NOTE Confidence: 0.91529736

00:04:32.275 --> 00:04:33.575 we've gone about this.

NOTE Confidence: 0.91529736

00:04:33.580 --> 00:04:34.067 Actually,

NOTE Confidence: 0.91529736

00:04:34.067 --> 00:04:36.015 starting with dissociative and

NOTE Confidence: 0.91529736

00:04:36.015 --> 00:04:38.450 bulk technologies that that let

NOTE Confidence: 0.908518037692308

00:04:38.527 --> 00:04:41.192 us down some some harder paths and

NOTE Confidence: 0.908518037692308

00:04:41.192 --> 00:04:43.508 moving forward to use new technologies

NOTE Confidence: 0.908518037692308

00:04:43.508 --> 00:04:45.243 that are really quite emergent.

NOTE Confidence: 0.908518037692308

00:04:45.250 --> 00:04:47.189 So that's the first story that I'll

NOTE Confidence: 0.908518037692308

00:04:47.189 --> 00:04:49.212 share with you and really will be

NOTE Confidence: 0.908518037692308

00:04:49.212 --> 00:04:50.910 the bulk of my discussion today.

NOTE Confidence: 0.908518037692308

00:04:50.910 --> 00:04:53.421 Why I won't speak to some of the approaches

NOTE Confidence: 0.908518037692308

00:04:53.421 --> 00:04:55.569 that we've developed to for example,

NOTE Confidence: 0.908518037692308

00:04:55.570 --> 00:04:57.435 product, chemotherapy benefit and and

NOTE Confidence: 0.908518037692308

00:04:57.435 --> 00:04:59.782 these are really based on epigenomic

NOTE Confidence: 0.908518037692308

00:04:59.782 --> 00:05:02.320 biomarkers that have emerged from large

NOTE Confidence: 0.908518037692308

00:05:02.320 --> 00:05:03.397 transcriptional profiling efforts

NOTE Confidence: 0.908518037692308

00:05:03.397 --> 00:05:05.910 but also coupled with in vitro data.

NOTE Confidence: 0.908518037692308

00:05:05.910 --> 00:05:07.878 But this is of course another area of

NOTE Confidence: 0.908518037692308

00:05:07.878 --> 00:05:09.688 interest and I think that as we think

NOTE Confidence: 0.908518037692308

00:05:09.688 --> 00:05:11.421 about personalizing therapy again,

NOTE Confidence: 0.908518037692308

00:05:11.421 --> 00:05:14.463 we must be cognizant about how

NOTE Confidence: 0.908518037692308

00:05:14.463 --> 00:05:17.367 we do this for standard of care

NOTE Confidence: 0.908518037692308

00:05:17.367 --> 00:05:19.243 chemotherapeutic agents and really

NOTE Confidence: 0.908518037692308

00:05:19.243 --> 00:05:20.650 deescalating whenever possible.

NOTE Confidence: 0.908518037692308

00:05:20.650 --> 00:05:23.920 And of course. Escalating when necessary.

NOTE Confidence: 0.908518037692308

00:05:23.920 --> 00:05:26.336 I will try to close and and really

NOTE Confidence: 0.908518037692308

00:05:26.336 --> 00:05:29.091 speak to some of our other efforts

NOTE Confidence: 0.908518037692308

00:05:29.091 --> 00:05:31.166 that have been leveraging genomic

NOTE Confidence: 0.908518037692308

00:05:31.238 --> 00:05:33.418 biomarkers to guide therapy selection

NOTE Confidence: 0.908518037692308

00:05:33.418 --> 00:05:36.260 and high risk of relapse breast cancer

NOTE Confidence: 0.908518037692308

00:05:36.260 --> 00:05:38.900 and I'll just touch on some of the

NOTE Confidence: 0.908518037692308

00:05:38.977 --> 00:05:41.371 work that was foundational for this

NOTE Confidence: 0.908518037692308

00:05:41.371 --> 00:05:43.938 and our ongoing trials in this area.

NOTE Confidence: 0.908518037692308

00:05:43.940 --> 00:05:44.286 Right,

NOTE Confidence: 0.908518037692308

00:05:44.286 --> 00:05:47.054 so I think it goes without saying that

NOTE Confidence: 0.908518037692308

00:05:47.054 --> 00:05:49.464 really her two positive breast cancer

NOTE Confidence: 0.908518037692308

00:05:49.464 --> 00:05:52.130 is an archetype for precision medicine.

NOTE Confidence: 0.908518037692308

00:05:52.130 --> 00:05:54.026 This is of course one of our first

NOTE Confidence: 0.908518037692308

00:05:54.026 --> 00:05:55.538 exemplars where we had a targeted

NOTE Confidence: 0.908518037692308

00:05:55.538 --> 00:05:56.773 therapy for this copy number,

NOTE Confidence: 0.908518037692308

00:05:56.780 --> 00:05:58.548 amplified subgroup of disease,

NOTE Confidence: 0.908518037692308

00:05:58.548 --> 00:06:01.788 and we know that trustees map has

NOTE Confidence: 0.908518037692308

00:06:01.788 --> 00:06:03.816 been tremendously effective and

NOTE Confidence: 0.908518037692308

00:06:03.816 --> 00:06:05.337 has really changed.

NOTE Confidence: 0.908518037692308

00:06:05.340 --> 00:06:06.972 The landscape and outcomes

NOTE Confidence: 0.908518037692308

00:06:06.972 --> 00:06:08.196 for these patients.

NOTE Confidence: 0.908518037692308

00:06:08.200 --> 00:06:09.384 It's still the case,

NOTE Confidence: 0.908518037692308

00:06:09.384 --> 00:06:09.680 however,

NOTE Confidence: 0.908518037692308

00:06:09.680 --> 00:06:12.770 that despite the effectiveness of this

NOTE Confidence: 0.908518037692308

00:06:12.770 --> 00:06:14.556 agent that a subset of patients recur,

NOTE Confidence: 0.908518037692308

00:06:14.560 --> 00:06:16.420 and this has really led then.

NOTE Confidence: 0.908518037692308

00:06:16.420 --> 00:06:19.102 Down a path of developing a

NOTE Confidence: 0.908518037692308

00:06:19.102 --> 00:06:21.647 number of additional FDA approved

NOTE Confidence: 0.908518037692308

00:06:21.647 --> 00:06:24.327 agents including purchase Mab,

NOTE Confidence: 0.908518037692308

00:06:24.330 --> 00:06:24.706 TDM,

NOTE Confidence: 0.908518037692308

00:06:24.706 --> 00:06:26.962 one as well as small molecule

NOTE Confidence: 0.908518037692308

00:06:26.962 --> 00:06:29.499 inhibitors such as Neurontin and Pat

NOTE Confidence: 0.908518037692308

00:06:29.499 --> 00:06:31.719 nib to overcome this resistance,

NOTE Confidence: 0.908518037692308

00:06:31.720 --> 00:06:33.025 and so there's been numerous

NOTE Confidence: 0.908518037692308

00:06:33.025 --> 00:06:34.069 efforts in this area.

NOTE Confidence: 0.908518037692308

00:06:34.070 --> 00:06:36.247 We now have a wealth of FDA

NOTE Confidence: 0.908518037692308

00:06:36.247 --> 00:06:37.905 approved drugs and of course,

NOTE Confidence: 0.908518037692308

00:06:37.905 --> 00:06:39.285 in tandem to this.

NOTE Confidence: 0.908518037692308

00:06:39.290 --> 00:06:41.486 There have been considerable efforts to

NOTE Confidence: 0.908518037692308

00:06:41.486 --> 00:06:43.944 start to understand the mechanisms of

NOTE Confidence: 0.908518037692308

00:06:43.944 --> 00:06:45.978 resistance convergence on PR3 kinase.

NOTE Confidence: 0.908518037692308

00:06:45.978 --> 00:06:47.938 Pathway involvement of P-10 and

NOTE Confidence: 0.908518037692308

00:06:47.938 --> 00:06:50.716 so forth and and two dissect the

NOTE Confidence: 0.908518037692308

00:06:50.716 --> 00:06:52.720 contribution of these pathways to

NOTE Confidence: 0.908518037692308

00:06:52.720 --> 00:06:54.690 resistance and her two positive

NOTE Confidence: 0.908518037692308

00:06:54.690 --> 00:06:55.478 breast cancer.

NOTE Confidence: 0.908518037692308

00:06:55.480 --> 00:06:57.536 But really sort of coming back to this.

NOTE Confidence: 0.908518037692308

00:06:57.540 --> 00:06:58.998 It's still the case that while

NOTE Confidence: 0.908518037692308

00:06:58.998 --> 00:07:00.557 we need to escalate therapy for

NOTE Confidence: 0.908518037692308

00:07:00.557 --> 00:07:01.625 a subset of patients,

NOTE Confidence: 0.908518037692308

00:07:01.630 --> 00:07:04.358 there may be a subset of patients who

NOTE Confidence: 0.908518037692308

00:07:04.358 --> 00:07:06.850 actually do not require chemotherapy,

NOTE Confidence: 0.908518037692308

00:07:06.850 --> 00:07:08.686 and who could be spared these

NOTE Confidence: 0.908518037692308

00:07:08.686 --> 00:07:09.910 agents and so really,

NOTE Confidence: 0.908518037692308

00:07:09.910 --> 00:07:11.722 this sort of highlights the very

NOTE Confidence: 0.908518037692308

00:07:11.722 --> 00:07:13.644 critical need at this point in

NOTE Confidence: 0.908518037692308

00:07:13.644 --> 00:07:15.269 time to develop predictive mile

NOTE Confidence: 0.908518037692308

00:07:15.269 --> 00:07:16.750 markers to tailor therapy.

NOTE Confidence: 0.908518037692308

00:07:16.750 --> 00:07:20.910 And this is both for escalation but also

NOTE Confidence: 0.908518037692308

00:07:20.910 --> 00:07:23.430 deescalation and so just to highlight,

NOTE Confidence: 0.908518037692308

00:07:23.430 --> 00:07:25.296 you know how important this is.

NOTE Confidence: 0.908518037692308

00:07:25.300 --> 00:07:28.302 I I thought I would just demonstrate some

NOTE Confidence: 0.908518037692308

00:07:28.302 --> 00:07:30.759 of the pivotal trials in this space.

NOTE Confidence: 0.908518037692308

00:07:30.760 --> 00:07:32.672 Of course, NSA, BP,

NOTE Confidence: 0.908518037692308

00:07:32.672 --> 00:07:33.150 B31,

NOTE Confidence: 0.908518037692308

00:07:33.150 --> 00:07:35.134 amongst others that demonstrated

NOTE Confidence: 0.908518037692308

00:07:35.134 --> 00:07:37.930 the benefit of trustees Mab with

NOTE Confidence: 0.908518037692308

00:07:37.930 --> 00:07:39.480 respect to disease free survival.

NOTE Confidence: 0.908518037692308

00:07:39.480 --> 00:07:41.025 But since this time there's

NOTE Confidence: 0.908518037692308

00:07:41.025 --> 00:07:42.570 been numerous studies that have

NOTE Confidence: 0.942298251333333

00:07:42.625 --> 00:07:44.460 sought to further escalate therapy.

NOTE Confidence: 0.942298251333333

00:07:44.460 --> 00:07:46.914 These include the affinity trial of

NOTE Confidence: 0.942298251333333

00:07:46.914 --> 00:07:49.232 adjuvant trustees map in combination

NOTE Confidence: 0.942298251333333

00:07:49.232 --> 00:07:51.968 with pertuzumab as well as the

NOTE Confidence: 0.942298251333333

00:07:51.968 --> 00:07:53.476 Katherine trial which compared

NOTE Confidence: 0.942298251333333

00:07:53.476 --> 00:07:56.117 T DM one versus trustees map.

NOTE Confidence: 0.942298251333333

00:07:56.120 --> 00:07:58.526 And so really critical studies in

NOTE Confidence: 0.942298251333333

00:07:58.526 --> 00:08:00.846 the field have been highlighted

NOTE Confidence: 0.942298251333333

00:08:00.846 --> 00:08:05.290 very recently at ASCO and in tandem.

NOTE Confidence: 0.942298251333333

00:08:05.290 --> 00:08:07.204 There have been efforts to deescalate

NOTE Confidence: 0.942298251333333

00:08:07.204 --> 00:08:09.702 therapy and and one example of this is

NOTE Confidence: 0.942298251333333

00:08:09.702 --> 00:08:12.010 the a peachy trial which examined adjutant.

NOTE Confidence: 0.942298251333333

00:08:12.010 --> 00:08:14.010 Paclitaxel plus trustees map but

NOTE Confidence: 0.942298251333333

00:08:14.010 --> 00:08:15.610 with omission of chemotherapy,

NOTE Confidence: 0.942298251333333

00:08:15.610 --> 00:08:16.220 mainly anthracyclines.

NOTE Confidence: 0.942298251333333

00:08:16.220 --> 00:08:18.660 So this is a huge area and there's

NOTE Confidence: 0.942298251333333

00:08:18.713 --> 00:08:20.918 a lot happening in this space to

NOTE Confidence: 0.942298251333333

00:08:20.918 --> 00:08:22.209 really personalize therapy and

NOTE Confidence: 0.942298251333333

00:08:22.209 --> 00:08:24.582 in part enabled by by the many

NOTE Confidence: 0.942298251333333

00:08:24.582 --> 00:08:26.018 therapeutic options we do have.

NOTE Confidence: 0.942298251333333

00:08:26.020 --> 00:08:27.142 So I don't expect you to

NOTE Confidence: 0.942298251333333

00:08:27.142 --> 00:08:28.140 read this slide over here,

NOTE Confidence: 0.942298251333333

00:08:28.140 --> 00:08:31.015 but I want to say that this is really

NOTE Confidence: 0.942298251333333

00:08:31.015 --> 00:08:33.325 a place where there's been just

NOTE Confidence: 0.942298251333333

00:08:33.325 --> 00:08:35.230 tremendous efforts spanning multiple

NOTE Confidence: 0.942298251333333

00:08:35.230 --> 00:08:38.116 neoadjuvant trials in the early stage.

NOTE Confidence: 0.942298251333333

00:08:38.120 --> 00:08:40.563 Her two positive setting looking at both

NOTE Confidence: 0.942298251333333

00:08:40.563 --> 00:08:43.099 single and or dual agent approaches,

NOTE Confidence: 0.942298251333333

00:08:43.100 --> 00:08:45.380 and of course a key goal and the

NOTE Confidence: 0.942298251333333

00:08:45.380 --> 00:08:46.842 correlative science that has been

NOTE Confidence: 0.942298251333333

00:08:46.842 --> 00:08:48.795 done in tandem has really focused on.

NOTE Confidence: 0.942298251333333

00:08:48.800 --> 00:08:52.540 Can we develop predictive biomarkers?

NOTE Confidence: 0.942298251333333

00:08:52.540 --> 00:08:53.812 In the neoadjuvant setting,

NOTE Confidence: 0.942298251333333

00:08:53.812 --> 00:08:56.824 and so I'll just say that there's been a

NOTE Confidence: 0.942298251333333

00:08:56.824 --> 00:08:59.260 huge amount of sequencing of these cohorts.

NOTE Confidence: 0.942298251333333

00:08:59.260 --> 00:09:01.402 Calgb for 601 Pamela includes some of

NOTE Confidence: 0.942298251333333

00:09:01.402 --> 00:09:04.041 the most in depth data where there's

NOTE Confidence: 0.942298251333333

00:09:04.041 --> 00:09:06.519 been both EXO mandor targeted sequencing.

NOTE Confidence: 0.942298251333333

00:09:06.520 --> 00:09:08.330 There's been expression profiling some

NOTE Confidence: 0.942298251333333

00:09:08.330 --> 00:09:10.800 using arrays, some using RNA seek,

NOTE Confidence: 0.942298251333333

00:09:10.800 --> 00:09:12.975 really as discovery efforts to

NOTE Confidence: 0.942298251333333

00:09:12.975 --> 00:09:15.380 identify these biomarkers, and then,

NOTE Confidence: 0.942298251333333

00:09:15.380 --> 00:09:16.040 of course,

NOTE Confidence: 0.942298251333333

00:09:16.040 --> 00:09:18.437 a big component of embedded in that

NOTE Confidence: 0.942298251333333

00:09:18.437 --> 00:09:20.838 work has been the use and intrinsic

NOTE Confidence: 0.942298251333333

00:09:20.838 --> 00:09:23.090 subtyping or pan 50 based subtyping.

NOTE Confidence: 0.942298251333333

00:09:23.090 --> 00:09:25.386 To ask whether there is enrichment for

NOTE Confidence: 0.942298251333333

00:09:25.386 --> 00:09:27.728 the intrinsic subgroups and some of the

NOTE Confidence: 0.942298251333333

00:09:27.728 --> 00:09:29.348 associations that have been identified,

NOTE Confidence: 0.942298251333333

00:09:29.350 --> 00:09:31.260 there are an enrichment amongst

NOTE Confidence: 0.942298251333333

00:09:31.260 --> 00:09:34.266 responders in the her 2E or her two

NOTE Confidence: 0.942298251333333

00:09:34.266 --> 00:09:36.342 enriched group and then on treatment.

NOTE Confidence: 0.942298251333333

00:09:36.342 --> 00:09:38.430 As some of these trials have

NOTE Confidence: 0.942298251333333

00:09:38.503 --> 00:09:40.688 included a non treatment biopsy,

NOTE Confidence: 0.942298251333333

00:09:40.690 --> 00:09:42.522 there's been associations demonstrated

NOTE Confidence: 0.942298251333333

00:09:42.522 --> 00:09:45.950 between us which from her two enriched,

NOTE Confidence: 0.942298251333333

00:09:45.950 --> 00:09:46.814 for example,

NOTE Confidence: 0.942298251333333

00:09:46.814 --> 00:09:48.696 to normal like and so.

NOTE Confidence: 0.942298251333333

00:09:48.696 --> 00:09:50.747 This is clearly an important area where

NOTE Confidence: 0.942298251333333

00:09:50.747 --> 00:09:52.919 there's been numerous correlative studies.

NOTE Confidence: 0.942298251333333

00:09:52.920 --> 00:09:54.698 And then the other area that I

NOTE Confidence: 0.942298251333333

00:09:54.698 --> 00:09:56.842 that I also want to point out is

NOTE Confidence: 0.942298251333333

00:09:56.842 --> 00:09:59.596 that of course many have turned to

NOTE Confidence: 0.942298251333333

00:09:59.596 --> 00:10:01.552 assessment of tumor infiltrating

NOTE Confidence: 0.942298251333333

00:10:01.552 --> 00:10:03.873 lymphocytes or thiles in attempts

NOTE Confidence: 0.942298251333333

00:10:03.873 --> 00:10:06.411 to predict response to her two

NOTE Confidence: 0.942298251333333

00:10:06.411 --> 00:10:08.370 targeted therapy both at baseline

NOTE Confidence: 0.942298251333333

00:10:08.370 --> 00:10:11.208 and in a subset of trials on therapy.

NOTE Confidence: 0.942298251333333

00:10:11.208 --> 00:10:11.856 And so,

NOTE Confidence: 0.942298251333333

00:10:11.856 --> 00:10:14.789 just to speak a little bit more to that,

NOTE Confidence: 0.942298251333333

00:10:14.790 --> 00:10:17.456 this is one of the more recent studies

NOTE Confidence: 0.942298251333333

00:10:17.456 --> 00:10:19.628 that actually examined both the Pamela

NOTE Confidence: 0.942298251333333

00:10:19.628 --> 00:10:21.868 trial as well as the validation trial.

NOTE Confidence: 0.942298251333333

00:10:21.870 --> 00:10:24.026 And really, the goal was to ask,

NOTE Confidence: 0.942298251333333

00:10:24.030 --> 00:10:24.960 could we,

NOTE Confidence: 0.942298251333333

00:10:24.960 --> 00:10:25.890 for example,

NOTE Confidence: 0.942298251333333

00:10:25.890 --> 00:10:28.215 predict response to therapy and

NOTE Confidence: 0.942298251333333

00:10:28.215 --> 00:10:31.120 so just to highlight a few pieces

NOTE Confidence: 0.942298251333333

00:10:31.120 --> 00:10:33.260 of data from this study?

NOTE Confidence: 0.942298251333333

00:10:33.260 --> 00:10:36.540 And really one of the.

NOTE Confidence: 0.942298251333333

00:10:36.540 --> 00:10:39.600 If not further efforts to predict

NOTE Confidence: 0.942298251333333

00:10:39.600 --> 00:10:43.149 probably needs, but not at the moment.

NOTE Confidence: 0.942298251333333

00:10:43.150 --> 00:10:44.800 Sorry I hear some noise.

NOTE Confidence: 0.709592876666667

00:10:44.810 --> 00:10:46.280 Please please go on mute Susanna.

NOTE Confidence: 0.874880092

00:10:48.960 --> 00:10:51.235 Right so here really what they had

NOTE Confidence: 0.874880092

00:10:51.235 --> 00:10:53.671 done in this study was to assess

NOTE Confidence: 0.874880092

00:10:53.671 --> 00:10:56.690 tills at baseline, and at day 15.

NOTE Confidence: 0.874880092

00:10:56.690 --> 00:10:58.808 So this was our running biopsy

NOTE Confidence: 0.874880092

00:10:58.808 --> 00:10:59.867 prior to administration.

NOTE Confidence: 0.874880092

00:10:59.870 --> 00:11:01.470 Actually, of any chemotherapy it's

NOTE Confidence: 0.874880092

00:11:01.470 --> 00:11:03.070 not administered in this trial,

NOTE Confidence: 0.874880092

00:11:03.070 --> 00:11:04.897 and what you can look at is the change

NOTE Confidence: 0.874880092

00:11:04.897 --> 00:11:06.700 in tumor infiltrating lymphocytes,

NOTE Confidence: 0.874880092

00:11:06.700 --> 00:11:09.215 with orange showing an increase

NOTE Confidence: 0.874880092

00:11:09.215 --> 00:11:11.730 blew a decrease and stable,

NOTE Confidence: 0.874880092

00:11:11.730 --> 00:11:12.978 and in tandem in this study,

NOTE Confidence: 0.874880092

00:11:12.980 --> 00:11:14.904 they also actually examined

NOTE Confidence: 0.874880092

00:11:14.904 --> 00:11:15.866 tumor cellularity,

NOTE Confidence: 0.874880092

00:11:15.870 --> 00:11:17.767 and you can see some exemplars here.

NOTE Confidence: 0.874880092

00:11:17.770 --> 00:11:19.994 And so this really led to the development.

NOTE Confidence: 0.874880092

00:11:20.000 --> 00:11:22.513 Of an approach called cell till which

NOTE Confidence: 0.874880092

00:11:22.513 --> 00:11:24.364 attempts to combine the estimates

NOTE Confidence: 0.874880092

00:11:24.364 --> 00:11:26.482 based on tills with celularity you

NOTE Confidence: 0.874880092

00:11:26.482 --> 00:11:28.667 can see the area under the curve

NOTE Confidence: 0.874880092

00:11:28.667 --> 00:11:30.902 here about .7 in the panelist study.

NOTE Confidence: 0.874880092

00:11:30.902 --> 00:11:32.932 Actually it's higher for cellularity

NOTE Confidence: 0.874880092

00:11:32.932 --> 00:11:35.985 and so the goal was to sort of

NOTE Confidence: 0.874880092

00:11:35.985 --> 00:11:37.755 develop a combined classifier here,

NOTE Confidence: 0.874880092

00:11:37.760 --> 00:11:38.800 and this has really been.

NOTE Confidence: 0.874880092

00:11:38.800 --> 00:11:39.290 You know,

NOTE Confidence: 0.874880092

00:11:39.290 --> 00:11:41.005 one of the great successes in trying

NOTE Confidence: 0.874880092

00:11:41.005 --> 00:11:42.923 to predict response to her two targeted

NOTE Confidence: 0.874880092

00:11:42.923 --> 00:11:44.873 therapy all be it with variable

NOTE Confidence: 0.874880092

00:11:44.873 --> 00:11:46.505 responses across different cohorts.

NOTE Confidence: 0.874880092

00:11:46.510 --> 00:11:48.309 And so I'll just show that when

NOTE Confidence: 0.874880092

00:11:48.309 --> 00:11:50.119 this group went on to corroborate.

NOTE Confidence: 0.874880092

00:11:50.120 --> 00:11:52.376 These findings in the LPT trial.

NOTE Confidence: 0.874880092

00:11:52.380 --> 00:11:55.677 You can see that the performance was

NOTE Confidence: 0.874880092

00:11:55.680 --> 00:11:57.550 substantially inferior with an AUC

NOTE Confidence: 0.874880092

00:11:57.550 --> 00:12:00.044 under .7 using cell till here and

NOTE Confidence: 0.874880092

00:12:00.044 --> 00:12:02.276 so this shows you one of the recent

NOTE Confidence: 0.874880092

00:12:02.340 --> 00:12:04.776 attempts and of course this group

NOTE Confidence: 0.874880092

00:12:04.776 --> 00:12:07.310 probably needs no introduction to the

NOTE Confidence: 0.874880092

00:12:07.310 --> 00:12:09.130 opportunities and challenges around

NOTE Confidence: 0.874880092

00:12:09.130 --> 00:12:10.950 scoring tumor infiltrating lymphocytes

NOTE Confidence: 0.874880092

00:12:11.012 --> 00:12:13.147 and really standardizing these assays.

NOTE Confidence: 0.874880092

00:12:13.150 --> 00:12:14.742 But I wanted to present this to set

NOTE Confidence: 0.874880092

00:12:14.742 --> 00:12:16.297 the stage sort of for where the fields

NOTE Confidence: 0.874880092

00:12:16.297 --> 00:12:18.018 at and to say that you know really,

NOTE Confidence: 0.874880092

00:12:18.020 --> 00:12:19.808 despite many many attempts.

NOTE Confidence: 0.874880092

00:12:19.808 --> 00:12:22.043 To develop predictive biomarkers from

NOTE Confidence: 0.874880092

00:12:22.043 --> 00:12:24.628 the genomic from the transcriptomic,

NOTE Confidence: 0.874880092

00:12:24.630 --> 00:12:26.863 we still do not have a validated

NOTE Confidence: 0.874880092

00:12:26.863 --> 00:12:28.530 predictive biomarker and sell tools

NOTE Confidence: 0.874880092

00:12:28.530 --> 00:12:30.165 have emerged in the forefront.

NOTE Confidence: 0.874880092

00:12:30.170 --> 00:12:32.778 But there's more work to be done to

NOTE Confidence: 0.874880092

00:12:32.778 --> 00:12:35.139 really ask how consistent this is.

NOTE Confidence: 0.874880092

00:12:35.140 --> 00:12:36.655 Also across different agents and

NOTE Confidence: 0.874880092

00:12:36.655 --> 00:12:38.775 so this really sets the stage for

NOTE Confidence: 0.874880092

00:12:38.775 --> 00:12:39.588 where we began.

NOTE Confidence: 0.874880092

00:12:39.590 --> 00:12:40.890 Our journey in this field,

NOTE Confidence: 0.874880092

00:12:40.890 --> 00:12:44.064 which was a collaboration with Sarah

NOTE Confidence: 0.874880092

00:12:44.064 --> 00:12:46.916 Hurvitz and Dennis Slamon at UCLA

NOTE Confidence: 0.874880092

00:12:46.916 --> 00:12:49.178 on the trio USB 07 clinical trial.

NOTE Confidence: 0.874880092

00:12:49.178 --> 00:12:50.788 Now this trial looked at

NOTE Confidence: 0.874880092

00:12:50.788 --> 00:12:51.660 neoadjuvant trustees.

NOTE Confidence: 0.874880092

00:12:51.660 --> 00:12:53.376 Vanderlip at mid in early stage

NOTE Confidence: 0.874880092

00:12:53.376 --> 00:12:54.940 her two positive breast cancer.

NOTE Confidence: 0.874880092

00:12:54.940 --> 00:12:57.320 It was an investigator initiated

NOTE Confidence: 0.874880092

00:12:57.320 --> 00:13:00.040 trial and here you can see the sort

NOTE Confidence: 0.874880092

00:13:00.040 --> 00:13:02.056 of sample size is 130 patients.

NOTE Confidence: 0.874880092

00:13:02.056 --> 00:13:04.982 They were assigned either to our one

NOTE Confidence: 0.874880092

00:13:04.982 --> 00:13:07.601 trustees Mobileone ARM 2 lapatinib or

NOTE Confidence: 0.874880092

00:13:07.601 --> 00:13:10.044 the combination and what was you know,

NOTE Confidence: 0.874880092

00:13:10.044 --> 00:13:11.790 really intriguing to me about this

NOTE Confidence: 0.874880092

00:13:11.853 --> 00:13:13.665 trial was that core biopsies were

NOTE Confidence: 0.874880092

00:13:13.665 --> 00:13:15.509 collected not only at baseline but

NOTE Confidence: 0.874880092

00:13:15.509 --> 00:13:17.511 actually at run in after a single

NOTE Confidence: 0.874880092

00:13:17.511 --> 00:13:19.636 cycle of targeted therapy alone.

NOTE Confidence: 0.874880092

00:13:19.636 --> 00:13:22.390 Prior to the administration of chemotherapy.

NOTE Confidence: 0.874880092

00:13:22.390 --> 00:13:24.178 Now you can see the pathologic

NOTE Confidence: 0.874880092

00:13:24.178 --> 00:13:25.072 complete response rates,

NOTE Confidence: 0.874880092

00:13:25.080 --> 00:13:27.774 which was the primary endpoint here of 47%.

NOTE Confidence: 0.874880092

00:13:27.774 --> 00:13:29.902 The PATNAM was inferior here as it

NOTE Confidence: 0.874880092

00:13:29.902 --> 00:13:32.515 has been in other trials and the

NOTE Confidence: 0.874880092

00:13:32.515 --> 00:13:34.450 combination was modestly improved but

NOTE Confidence: 0.874880092

00:13:34.515 --> 00:13:37.179 not statistically significantly different,

NOTE Confidence: 0.874880092

00:13:37.180 --> 00:13:39.530 and so really this is this trial

NOTE Confidence: 0.874880092

00:13:39.530 --> 00:13:41.090 is distinct in the collection of

NOTE Confidence: 0.874880092

00:13:41.090 --> 00:13:42.962 a non treatment core biopsy prior

NOTE Confidence: 0.874880092

00:13:42.962 --> 00:13:44.906 to administration of chemo and at

NOTE Confidence: 0.907119852

00:13:44.960 --> 00:13:46.745 the time I felt that this would

NOTE Confidence: 0.907119852

00:13:46.745 --> 00:13:48.540 really afford us some unique

NOTE Confidence: 0.907119852

00:13:48.540 --> 00:13:50.600 insights into biomarkers of

NOTE Confidence: 0.907119852

00:13:50.600 --> 00:13:52.660 response after targeted therapy.

NOTE Confidence: 0.907119852

00:13:52.660 --> 00:13:54.940 Alone without having to deconvolve

NOTE Confidence: 0.907119852

00:13:54.940 --> 00:13:57.288 the effects of chemotherapy and so

NOTE Confidence: 0.907119852

00:13:57.288 --> 00:13:59.101 in initial work that was led by

NOTE Confidence: 0.907119852

00:13:59.101 --> 00:14:01.079 Sarah Hurvitz and Jennifer Castle,

NOTE Confidence: 0.907119852

00:14:01.080 --> 00:14:02.879 Gin a former fellow in my lab.

NOTE Confidence: 0.907119852

00:14:02.880 --> 00:14:04.712 Now, faculty at Stanford,

NOTE Confidence: 0.907119852

00:14:04.712 --> 00:14:07.460 we had embarked on an initiative,

NOTE Confidence: 0.907119852

00:14:07.460 --> 00:14:10.108 and this was actually embedded in the B

NOTE Confidence: 0.907119852

00:14:10.108 --> 00:14:12.977 07 trial design to leverage these pre

NOTE Confidence: 0.907119852

00:14:12.977 --> 00:14:15.535 on treatment and surgical samples to

NOTE Confidence: 0.907119852

00:14:15.535 --> 00:14:17.996 conduct bulk RNA expression profiling.

NOTE Confidence: 0.907119852

00:14:17.996 --> 00:14:20.641 And this was done using

NOTE Confidence: 0.907119852

00:14:20.641 --> 00:14:23.189 actually dual color microarrays.

NOTE Confidence: 0.907119852

00:14:23.190 --> 00:14:25.110 Which have now been largely

NOTE Confidence: 0.907119852

00:14:25.110 --> 00:14:26.646 supplanted by by RDC,

NOTE Confidence: 0.907119852

00:14:26.650 --> 00:14:27.943 but nonetheless you.

NOTE Confidence: 0.907119852

00:14:27.943 --> 00:14:31.130 You can see here the sort of try the

NOTE Confidence: 0.907119852

00:14:31.130 --> 00:14:34.260 design for this after a single cycle of

NOTE Confidence: 0.907119852

00:14:34.260 --> 00:14:36.708 of either of these agents we collected

NOTE Confidence: 0.907119852

00:14:36.708 --> 00:14:38.327 actually fresh frozen material and

NOTE Confidence: 0.907119852

00:14:38.327 --> 00:14:40.167 this was from a total of 89 patients.

NOTE Confidence: 0.907119852

00:14:40.170 --> 00:14:42.030 The fresh frozen material was then

NOTE Confidence: 0.907119852

00:14:42.030 --> 00:14:44.011 sent for RNA profiling and so of

NOTE Confidence: 0.907119852

00:14:44.011 --> 00:14:45.493 course the key question here is

NOTE Confidence: 0.907119852

00:14:45.493 --> 00:14:47.329 based on these expression profiles,

NOTE Confidence: 0.907119852

00:14:47.330 --> 00:14:49.954 could we predict pathologic

NOTE Confidence: 0.907119852

00:14:49.954 --> 00:14:51.610 complete response and?

NOTE Confidence: 0.907119852

00:14:51.610 --> 00:14:53.990 You can see that we took actually

NOTE Confidence: 0.907119852

00:14:53.990 --> 00:14:56.841 quite a deep dive into understanding

NOTE Confidence: 0.907119852

00:14:56.841 --> 00:14:59.461 the baseline clinical covariates and

NOTE Confidence: 0.907119852

00:14:59.461 --> 00:15:02.360 tumor features for these individuals.

NOTE Confidence: 0.907119852

00:15:02.360 --> 00:15:04.215 What you can see are the different

NOTE Confidence: 0.907119852

00:15:04.215 --> 00:15:05.290 measurements that were made.

NOTE Confidence: 0.907119852

00:15:05.290 --> 00:15:07.537 These include the her two fish ratio,

NOTE Confidence: 0.907119852

00:15:07.540 --> 00:15:09.600 which was.

NOTE Confidence: 0.907119852

00:15:09.600 --> 00:15:11.155 Obviously performed as part of

NOTE Confidence: 0.907119852

00:15:11.155 --> 00:15:12.399 the enrollment crunch cereal.

NOTE Confidence: 0.907119852

00:15:12.400 --> 00:15:14.836 We then went on to calculate

NOTE Confidence: 0.907119852

00:15:14.836 --> 00:15:16.054 the immune score.

NOTE Confidence: 0.907119852

00:15:16.060 --> 00:15:17.956 Her two IHC was also performed.

NOTE Confidence: 0.907119852

00:15:17.960 --> 00:15:20.198 Tills were scored and based on

NOTE Confidence: 0.907119852

00:15:20.198 --> 00:15:21.690 the RNA expression profiling,

NOTE Confidence: 0.907119852

00:15:21.690 --> 00:15:23.484 we were able to infer both

NOTE Confidence: 0.907119852

00:15:23.484 --> 00:15:25.440 intrinsic subtype M50 as well as

NOTE Confidence: 0.907119852

00:15:25.440 --> 00:15:26.844 the integrative subtypes which

NOTE Confidence: 0.907119852

00:15:26.844 --> 00:15:28.900 my group defined some years ago,

NOTE Confidence: 0.907119852

00:15:28.900 --> 00:15:30.636 and I'll speak to that more later

NOTE Confidence: 0.907119852

00:15:30.640 --> 00:15:32.146 and and then you have hormone

NOTE Confidence: 0.907119852

00:15:32.146 --> 00:15:33.540 receptor status and of course,

NOTE Confidence: 0.907119852

00:15:33.540 --> 00:15:34.674 Pathologic complete response.

NOTE Confidence: 0.907119852

00:15:34.674 --> 00:15:37.818 So really quite a rich data set with

NOTE Confidence: 0.907119852

00:15:37.818 --> 00:15:39.402 with numerous molecular correlate's.

NOTE Confidence: 0.907119852

00:15:39.402 --> 00:15:41.658 I'll cut to the chase and say that

NOTE Confidence: 0.907119852

00:15:41.660 --> 00:15:44.124 despite having all of these in hand,

NOTE Confidence: 0.907119852

00:15:44.130 --> 00:15:46.505 really none of them were

NOTE Confidence: 0.907119852

00:15:46.505 --> 00:15:48.405 robustly predictive of PCR.

NOTE Confidence: 0.907119852

00:15:48.410 --> 00:15:50.372 And that was true both at

NOTE Confidence: 0.907119852

00:15:50.372 --> 00:15:52.559 baseline as well as on therapy.

NOTE Confidence: 0.907119852

00:15:52.560 --> 00:15:54.184 But what we did learn from this

NOTE Confidence: 0.907119852

00:15:54.184 --> 00:15:55.970 study is that we were able to

NOTE Confidence: 0.907119852

00:15:55.970 --> 00:15:57.518 really start to deconvolve some of

NOTE Confidence: 0.907119852

00:15:57.574 --> 00:15:58.874 the contributions and something

NOTE Confidence: 0.907119852

00:15:58.874 --> 00:16:00.824 and illuminate some of the real

NOTE Confidence: 0.907119852

00:16:00.830 --> 00:16:03.605 challenges that come up with

NOTE Confidence: 0.907119852

00:16:03.605 --> 00:16:05.825 bulk admic sequencing data,

NOTE Confidence: 0.907119852

00:16:05.830 --> 00:16:07.926 and so many of the patterns that we

NOTE Confidence: 0.907119852

00:16:07.926 --> 00:16:09.980 saw are in line with what might.

NOTE Confidence: 0.907119852

00:16:09.980 --> 00:16:12.360 One might expect So what this plot

NOTE Confidence: 0.907119852

00:16:12.360 --> 00:16:14.758 shows here is actually the changes

NOTE Confidence: 0.907119852

00:16:14.758 --> 00:16:16.923 in gene expression during the

NOTE Confidence: 0.907119852

00:16:16.923 --> 00:16:19.279 short term on treatment biopsy.

NOTE Confidence: 0.907119852

00:16:19.280 --> 00:16:21.653 So after just a single cycle you

NOTE Confidence: 0.907119852

00:16:21.653 --> 00:16:23.812 can see the normalized enrichment

NOTE Confidence: 0.907119852

00:16:23.812 --> 00:16:25.856 scores for a variety of gene sets,

NOTE Confidence: 0.907119852

00:16:25.860 --> 00:16:28.578 and amongst those that are downregulated

NOTE Confidence: 0.907119852

00:16:28.578 --> 00:16:31.906 we have decreases in her two signaling

NOTE Confidence: 0.907119852

00:16:31.906 --> 00:16:33.818 proliferation and so forth.

NOTE Confidence: 0.907119852

00:16:33.820 --> 00:16:37.292 In in contrast we see increased enrichment

NOTE Confidence: 0.907119852

00:16:37.292 --> 00:16:40.409 for stromal and immune signatures.

NOTE Confidence: 0.907119852

00:16:40.410 --> 00:16:41.535 Just started after the short

NOTE Confidence: 0.907119852

00:16:41.535 --> 00:16:42.660 term therapy and there's a

NOTE Confidence: 0.907119852

00:16:42.701 --> 00:16:43.969 variety of signatures included.

NOTE Confidence: 0.907119852

00:16:43.970 --> 00:16:46.007 Many of them are of course correlated,

NOTE Confidence: 0.907119852

00:16:46.010 --> 00:16:47.730 and that's actually something that's

NOTE Confidence: 0.907119852

00:16:47.730 --> 00:16:49.801 really important to examine as we

NOTE Confidence: 0.907119852

00:16:49.801 --> 00:16:51.256 seek to parse these signatures,

NOTE Confidence: 0.912750056111111

00:16:51.260 --> 00:16:53.980 and so this is just showing really the

NOTE Confidence: 0.912750056111111

00:16:53.980 --> 00:16:55.482 Pearson correlation coefficient matrix

NOTE Confidence: 0.912750056111111

00:16:55.482 --> 00:16:57.768 based on the gene set enrichment,

NOTE Confidence: 0.912750056111111

00:16:57.770 --> 00:16:59.660 and hopefully what you can take away

NOTE Confidence: 0.912750056111111

00:16:59.660 --> 00:17:01.701 from this is that there's a huge

NOTE Confidence: 0.912750056111111

00:17:01.701 --> 00:17:03.453 degree of correlation for many of

NOTE Confidence: 0.912750056111111

00:17:03.516 --> 00:17:05.043 these pathways with one another,

NOTE Confidence: 0.912750056111111

00:17:05.043 --> 00:17:06.549 and this just sort of mirrors

NOTE Confidence: 0.912750056111111

00:17:06.549 --> 00:17:08.302 what we see over here. So indeed,

NOTE Confidence: 0.912750056111111

00:17:08.302 --> 00:17:10.514 in this short time course we are.

NOTE Confidence: 0.912750056111111

00:17:10.520 --> 00:17:11.970 Observing a number of patterns

NOTE Confidence: 0.912750056111111

00:17:11.970 --> 00:17:13.690 that we might expect to see.

NOTE Confidence: 0.88754812

00:17:15.740 --> 00:17:16.600 But there are, you know,

NOTE Confidence: 0.88754812

00:17:16.600 --> 00:17:18.742 we can also use these data to start to

NOTE Confidence: 0.88754812

00:17:18.742 --> 00:17:20.200 deconvolve what happens on therapy,

NOTE Confidence: 0.88754812

00:17:20.200 --> 00:17:22.040 and so, like many others,

NOTE Confidence: 0.88754812

00:17:22.040 --> 00:17:24.640 we also performed intrinsic subtyping.

NOTE Confidence: 0.88754812

00:17:24.640 --> 00:17:26.236 You can see that there's a preponderance

NOTE Confidence: 0.88754812

00:17:26.236 --> 00:17:27.960 of the her two enriched subgroup.

NOTE Confidence: 0.88754812

00:17:27.960 --> 00:17:30.112 This comprises roughly 53%

NOTE Confidence: 0.88754812

00:17:30.112 --> 00:17:31.726 of patients pretreatment.

NOTE Confidence: 0.88754812

00:17:31.730 --> 00:17:33.420 There's also a substantial normal,

NOTE Confidence: 0.88754812

00:17:33.420 --> 00:17:36.400 like composition here at treat.

NOTE Confidence: 0.88754812

00:17:36.400 --> 00:17:38.863 You know, prior to therapy, but on therapy,

NOTE Confidence: 0.88754812

00:17:38.863 --> 00:17:40.760 we do see this pretty dramatic switching,

NOTE Confidence: 0.88754812

00:17:40.760 --> 00:17:42.699 where a number of the her 2E

NOTE Confidence: 0.88754812

00:17:42.699 --> 00:17:44.200 cases actually become normalized.

NOTE Confidence: 0.88754812

00:17:44.200 --> 00:17:45.790 There is some other switching

NOTE Confidence: 0.88754812

00:17:45.790 --> 00:17:46.744 going on amongst.

NOTE Confidence: 0.88754812

00:17:46.750 --> 00:17:48.490 Luminous, but that's more modest,

NOTE Confidence: 0.88754812

00:17:48.490 --> 00:17:49.850 so we can assess these,

NOTE Confidence: 0.88754812

00:17:49.850 --> 00:17:51.452 and in these patterns are in

NOTE Confidence: 0.88754812

00:17:51.452 --> 00:17:52.916 line where others have reported

NOTE Confidence: 0.88754812

00:17:52.916 --> 00:17:54.616 and Pamela and similar trials.

NOTE Confidence: 0.88754812

00:17:54.620 --> 00:17:57.581 We can also use the bulk data to attempt

NOTE Confidence: 0.88754812

00:17:57.581 --> 00:18:00.597 to deconvolve the immune composition,

NOTE Confidence: 0.88754812

00:18:00.600 --> 00:18:03.694 but this is an exceedingly hard task,

NOTE Confidence: 0.88754812

00:18:03.700 --> 00:18:04.284 really, uh,

NOTE Confidence: 0.88754812

00:18:04.284 --> 00:18:06.620 you know there are many algorithms for this.

NOTE Confidence: 0.88754812

00:18:06.620 --> 00:18:08.204 I show one example,

NOTE Confidence: 0.88754812

00:18:08.204 --> 00:18:09.788 the cyber sort approach,

NOTE Confidence: 0.88754812

00:18:09.790 --> 00:18:11.330 which uses a reference matrix,

NOTE Confidence: 0.88754812

00:18:11.330 --> 00:18:13.175 and what I hope you take away from this

NOTE Confidence: 0.88754812

00:18:13.175 --> 00:18:15.426 is that you know apparent from these

NOTE Confidence: 0.88754812

00:18:15.426 --> 00:18:16.754 plots there's actually relatively.

NOTE Confidence: 0.88754812

00:18:16.760 --> 00:18:19.098 Modest changes from pre to on treatment

NOTE Confidence: 0.88754812

00:18:19.098 --> 00:18:22.238 or even at the time of definitive surgery.

NOTE Confidence: 0.88754812

00:18:22.240 --> 00:18:24.540 After completion of both

NOTE Confidence: 0.88754812

00:18:24.540 --> 00:18:26.265 targeted and chemotherapy.

NOTE Confidence: 0.88754812

00:18:26.270 --> 00:18:29.358 So this is a hard nut to crack.

NOTE Confidence: 0.88754812

00:18:29.360 --> 00:18:31.380 And actually the admixture

NOTE Confidence: 0.88754812

00:18:31.380 --> 00:18:32.895 in these populations.

NOTE Confidence: 0.88754812

00:18:32.900 --> 00:18:34.229 Really, we believe,

NOTE Confidence: 0.88754812

00:18:34.229 --> 00:18:36.444 hindered our ability to discover

NOTE Confidence: 0.88754812

00:18:36.444 --> 00:18:38.280 biomarkers in this context,

NOTE Confidence: 0.88754812

00:18:38.280 --> 00:18:39.786 and so I'll leave off there

NOTE Confidence: 0.88754812

00:18:39.786 --> 00:18:41.409 and say that this in tandem.

NOTE Confidence: 0.88754812

00:18:41.410 --> 00:18:41.778 You know,

NOTE Confidence: 0.88754812

00:18:41.778 --> 00:18:43.066 having sort of early reads into this

NOTE Confidence: 0.88754812

00:18:43.066 --> 00:18:44.440 and what others had been observing,

NOTE Confidence: 0.88754812

00:18:44.440 --> 00:18:45.955 which was similar.

NOTE Confidence: 0.88754812

00:18:45.955 --> 00:18:47.470 Let us too.

NOTE Confidence: 0.88754812

00:18:47.470 --> 00:18:49.955 Then take a new approach and so

NOTE Confidence: 0.88754812

00:18:49.955 --> 00:18:51.618 in collaboration with ministering

NOTE Confidence: 0.88754812

00:18:51.618 --> 00:18:54.233 while they were developing the

NOTE Confidence: 0.88754812

00:18:54.233 --> 00:18:56.325 digital spatial profiling platform,

NOTE Confidence: 0.88754812

00:18:56.330 --> 00:18:57.474 we really embarked on.

NOTE Confidence: 0.88754812

00:18:57.474 --> 00:18:59.190 This study was led by Katherine

NOTE Confidence: 0.88754812

00:18:59.250 --> 00:19:00.099 McNamara and MD,

NOTE Confidence: 0.88754812

00:19:00.100 --> 00:19:02.130 PhD student,

NOTE Confidence: 0.88754812

00:19:02.130 --> 00:19:03.677 who will match very soon and and

NOTE Confidence: 0.88754812

00:19:03.677 --> 00:19:05.520 was just a stellar lead and really

NOTE Confidence: 0.88754812

00:19:05.520 --> 00:19:07.212 taking on these new data types.

NOTE Confidence: 0.88754812

00:19:07.220 --> 00:19:08.613 And So what we did was to

NOTE Confidence: 0.88754812

00:19:08.613 --> 00:19:09.940 go back to this cohort.

NOTE Confidence: 0.88754812

00:19:09.940 --> 00:19:11.620 Now we turn to the formalin,

NOTE Confidence: 0.88754812

00:19:11.620 --> 00:19:13.552 fixed paraffin embedded tissue

NOTE Confidence: 0.88754812

00:19:13.552 --> 00:19:16.450 and we selected data from a.

NOTE Confidence: 0.88754812

00:19:16.450 --> 00:19:18.322 You know it was a total of 100 and.

NOTE Confidence: 0.88754812

00:19:18.330 --> 00:19:20.150 There were 122 samples that

NOTE Confidence: 0.88754812

00:19:20.150 --> 00:19:21.606 derived from 57 patients,

NOTE Confidence: 0.88754812

00:19:21.610 --> 00:19:23.381 and these were the ones that we

NOTE Confidence: 0.88754812

00:19:23.381 --> 00:19:25.067 felt we had adequate material

NOTE Confidence: 0.88754812

00:19:25.067 --> 00:19:26.420 left for for this assay,

NOTE Confidence: 0.88754812

00:19:26.420 --> 00:19:28.110 and so there were a total of

NOTE Confidence: 0.88754812

00:19:28.110 --> 00:19:29.390 20 in the discovery cohort,

NOTE Confidence: 0.88754812

00:19:29.390 --> 00:19:30.990 29 in the validation,

NOTE Confidence: 0.88754812

00:19:30.990 --> 00:19:32.590 again sampled at baseline,

NOTE Confidence: 0.88754812

00:19:32.590 --> 00:19:36.188 pretreatment at run in and at surgery.

NOTE Confidence: 0.88754812

00:19:36.190 --> 00:19:36.579 Right,

NOTE Confidence: 0.88754812

00:19:36.579 --> 00:19:39.302 so for those of you that are

NOTE Confidence: 0.88754812

00:19:39.302 --> 00:19:41.459 not familiar with this assay,

NOTE Confidence: 0.88754812

00:19:41.460 --> 00:19:44.307 we were focused on the Multiplex

NOTE Confidence: 0.88754812

00:19:44.307 --> 00:19:45.341 proteomic piece.

NOTE Confidence: 0.88754812

00:19:45.341 --> 00:19:47.760 There are indeed also technologies

NOTE Confidence: 0.88754812

00:19:47.760 --> 00:19:49.860 that allow one to profile the

NOTE Confidence: 0.88754812

00:19:49.860 --> 00:19:51.542 transcriptome that we're still very

NOTE Confidence: 0.88754812

00:19:51.542 --> 00:19:53.264 much in development at this time.

NOTE Confidence: 0.88754812

00:19:53.270 --> 00:19:55.058 The basic premise of this assay

NOTE Confidence: 0.88754812

00:19:55.058 --> 00:19:57.033 is that we have an indexing

NOTE Confidence: 0.88754812

00:19:57.033 --> 00:19:58.813 oligo nucleotide that is attached

NOTE Confidence: 0.88754812

00:19:58.813 --> 00:20:00.390 to this UV linker,

NOTE Confidence: 0.88754812

00:20:00.390 --> 00:20:02.070 and So what we can essentially

NOTE Confidence: 0.88754812

00:20:02.070 --> 00:20:04.471 do is to sustain our slide or FP

NOTE Confidence: 0.88754812

00:20:04.471 --> 00:20:06.295 slide with probes or antibodies of.

NOTE Confidence: 0.88754812

00:20:06.300 --> 00:20:09.100 Interest these oligos are UV,

NOTE Confidence: 0.88754812

00:20:09.100 --> 00:20:09.374 photo,

NOTE Confidence: 0.88754812

00:20:09.374 --> 00:20:11.018 cleavable and so that we can

NOTE Confidence: 0.88754812

00:20:11.018 --> 00:20:11.840 image the slides.

NOTE Confidence: 0.825701003333333

00:20:11.840 --> 00:20:14.432 Go in and select regions of interest or

NOTE Confidence: 0.825701003333333

00:20:14.432 --> 00:20:16.960 our allies and cleave off these oligos,

NOTE Confidence: 0.825701003333333

00:20:16.960 --> 00:20:20.026 aspirate them, and especially dispense them,

NOTE Confidence: 0.825701003333333

00:20:20.030 --> 00:20:21.894 and then they can be read off digitally,

NOTE Confidence: 0.825701003333333

00:20:21.900 --> 00:20:23.364 either using the Nanostring

NOTE Confidence: 0.825701003333333

00:20:23.364 --> 00:20:25.194 encounter or indeed via sequencing.

NOTE Confidence: 0.825701003333333

00:20:25.200 --> 00:20:28.670 And this process is repeated for a number

NOTE Confidence: 0.825701003333333

00:20:28.670 --> 00:20:31.435 of antibodies up to approximately 40 Plex,

NOTE Confidence: 0.825701003333333

00:20:31.440 --> 00:20:34.020 and so to give you a flavor for what we did.

NOTE Confidence: 0.825701003333333

00:20:34.020 --> 00:20:35.305 These were all four Micron

NOTE Confidence: 0.825701003333333

00:20:35.305 --> 00:20:36.890 sections that we took from this.

NOTE Confidence: 0.825701003333333

00:20:36.890 --> 00:20:39.210 You know almost this clinical trial for which

NOTE Confidence: 0.825701003333333

00:20:39.210 --> 00:20:41.828 we were using the sort of residual material,

NOTE Confidence: 0.825701003333333

00:20:41.830 --> 00:20:44.518 and we actually arrayed the pre on and

NOTE Confidence: 0.825701003333333

00:20:44.518 --> 00:20:46.657 surgical sample onto the same slide

NOTE Confidence: 0.825701003333333

00:20:46.657 --> 00:20:48.788 to mitigate batch effects and went

NOTE Confidence: 0.825701003333333

00:20:48.788 --> 00:20:51.336 in then and essentially use one of

NOTE Confidence: 0.825701003333333

00:20:51.336 --> 00:20:54.332 the the features of DSP which is to

NOTE Confidence: 0.825701003333333

00:20:54.332 --> 00:20:56.194 select based on phenotypic markers,

NOTE Confidence: 0.825701003333333

00:20:56.194 --> 00:20:58.868 in this case pants ID keratin to

NOTE Confidence: 0.825701003333333

00:20:58.868 --> 00:21:01.822 enrich for tumor cells as well as CD

NOTE Confidence: 0.825701003333333

00:21:01.822 --> 00:21:05.272 45 to illuminate immune cells.

NOTE Confidence: 0.825701003333333

00:21:05.272 --> 00:21:06.888 And of course this is coupled with the.

NOTE Confidence: 0.825701003333333

00:21:06.890 --> 00:21:08.594 Does DNA marker and so we can go

NOTE Confidence: 0.825701003333333

00:21:08.594 --> 00:21:10.550 in and really then take the tumor,

NOTE Confidence: 0.825701003333333

00:21:10.550 --> 00:21:11.394 enrich mask,

NOTE Confidence: 0.825701003333333

00:21:11.394 --> 00:21:14.770 or indeed take the inverted mask and enrich

NOTE Confidence: 0.825701003333333

00:21:14.852 --> 00:21:16.486 for the surrounding microenvironment?

NOTE Confidence: 0.825701003333333

00:21:16.486 --> 00:21:20.910 And we profiled a 43 Plex marker panel.

NOTE Confidence: 0.825701003333333

00:21:20.910 --> 00:21:23.062 This was really the panel that was in

NOTE Confidence: 0.825701003333333

00:21:23.062 --> 00:21:24.850 development at Nanostring at the time.

NOTE Confidence: 0.825701003333333

00:21:24.850 --> 00:21:28.030 We were fortunate that included a

NOTE Confidence: 0.825701003333333

00:21:28.030 --> 00:21:31.042 number of her two pathway members,

NOTE Confidence: 0.825701003333333

00:21:31.042 --> 00:21:32.860 AKT Phospho, AKT, and so forth.

NOTE Confidence: 0.825701003333333

00:21:32.860 --> 00:21:34.450 We actually had to add her to on.

NOTE Confidence: 0.825701003333333

00:21:34.450 --> 00:21:36.298 We could not convince them at

NOTE Confidence: 0.825701003333333

00:21:36.298 --> 00:21:37.530 the time to add.

NOTE Confidence: 0.825701003333333

00:21:37.530 --> 00:21:39.410 IAR, which was you know,

NOTE Confidence: 0.825701003333333

00:21:39.410 --> 00:21:40.958 disappointing in many respects,

NOTE Confidence: 0.825701003333333

00:21:40.958 --> 00:21:43.695 but I think many of the immune markers

NOTE Confidence: 0.825701003333333

00:21:43.695 --> 00:21:45.270 are really well represented here,

NOTE Confidence: 0.825701003333333

00:21:45.270 --> 00:21:47.684 and so this is the panel that we had now,

NOTE Confidence: 0.825701003333333

00:21:47.684 --> 00:21:49.328 just to give you a flavor,

NOTE Confidence: 0.825701003333333

00:21:49.330 --> 00:21:51.046 you know our eyes select selection.

NOTE Confidence: 0.825701003333333

00:21:51.050 --> 00:21:52.400 We could spend a lot of time talking about.

NOTE Confidence: 0.825701003333333

00:21:52.400 --> 00:21:54.035 There are huge study design

NOTE Confidence: 0.825701003333333

00:21:54.035 --> 00:21:56.030 considerations for how we do this.

NOTE Confidence: 0.825701003333333

00:21:56.030 --> 00:21:56.834 You know,

NOTE Confidence: 0.825701003333333

00:21:56.834 --> 00:21:59.246 in this trial cohort we essentially

NOTE Confidence: 0.825701003333333

00:21:59.246 --> 00:22:01.749 our goal was to select an average

NOTE Confidence: 0.825701003333333

00:22:01.749 --> 00:22:03.657 of four or ROI's part issue.

NOTE Confidence: 0.825701003333333

00:22:03.657 --> 00:22:05.820 This shows you an example where we

NOTE Confidence: 0.825701003333333

00:22:05.882 --> 00:22:08.314 selected 6 and in a different case where.

NOTE Confidence: 0.825701003333333

00:22:08.320 --> 00:22:10.161 You can see three of the four

NOTE Confidence: 0.825701003333333

00:22:10.161 --> 00:22:11.599 in this non PCR case,

NOTE Confidence: 0.825701003333333

00:22:11.600 --> 00:22:13.598 so you know we are essentially

NOTE Confidence: 0.825701003333333

00:22:13.598 --> 00:22:14.597 picking similar regions,

NOTE Confidence: 0.825701003333333

00:22:14.600 --> 00:22:16.735 but trying to be representative here and

NOTE Confidence: 0.825701003333333

00:22:16.735 --> 00:22:18.960 there are many ways to go about doing

NOTE Confidence: 0.825701003333333

00:22:18.960 --> 00:22:20.985 this now just to convince ourselves

NOTE Confidence: 0.825701003333333

00:22:20.985 --> 00:22:23.123 that the technology was working because

NOTE Confidence: 0.825701003333333

00:22:23.123 --> 00:22:25.515 we were amongst the first to view this,

NOTE Confidence: 0.825701003333333

00:22:25.520 --> 00:22:28.772 we went in and compared the

NOTE Confidence: 0.825701003333333

00:22:28.772 --> 00:22:31.498 normalized DSP KY 67 levels with the

NOTE Confidence: 0.825701003333333

00:22:31.498 --> 00:22:33.578 immunohistochemistry CHI 67 that we had

NOTE Confidence: 0.825701003333333

00:22:33.578 --> 00:22:35.826 for the same subset of samples and you

NOTE Confidence: 0.825701003333333

00:22:35.898 --> 00:22:38.296 can see that the correlation is .62.

NOTE Confidence: 0.825701003333333

00:22:38.296 --> 00:22:39.664 Reasonably good here.

NOTE Confidence: 0.825701003333333

00:22:39.664 --> 00:22:42.792 We did a similar analysis for her

NOTE Confidence: 0.825701003333333

00:22:42.792 --> 00:22:44.770 to where we had compared with,

NOTE Confidence: 0.825701003333333

00:22:44.770 --> 00:22:45.510 you know,

NOTE Confidence: 0.825701003333333

00:22:45.510 --> 00:22:47.730 I see based staining and again

NOTE Confidence: 0.825701003333333

00:22:47.803 --> 00:22:50.143 we're seeing trends that we would

NOTE Confidence: 0.825701003333333

00:22:50.143 --> 00:22:51.980 expect that convinced us of.

NOTE Confidence: 0.825701003333333

00:22:51.980 --> 00:22:54.236 You know that we were at least reading

NOTE Confidence: 0.825701003333333

00:22:54.236 --> 00:22:56.180 out some of this appropriately.

NOTE Confidence: 0.825701003333333

00:22:56.180 --> 00:22:58.574 So to give you a sense for the data.

NOTE Confidence: 0.825701003333333

00:22:58.580 --> 00:22:58.936 Really,

NOTE Confidence: 0.825701003333333

00:22:58.936 --> 00:23:01.428 what you can see here are just

NOTE Confidence: 0.825701003333333

00:23:01.428 --> 00:23:02.140 two examples

NOTE Confidence: 0.846486428333333

00:23:02.211 --> 00:23:03.125 of case 69.

NOTE Confidence: 0.846486428333333

00:23:03.125 --> 00:23:06.100 A pathologic complete response and case 58.

NOTE Confidence: 0.846486428333333

00:23:06.100 --> 00:23:09.150 I'm showing you individual regions.

NOTE Confidence: 0.846486428333333

00:23:09.150 --> 00:23:10.206 That we went in and profiled,

NOTE Confidence: 0.846486428333333

00:23:10.210 --> 00:23:12.721 and you can see the her two levels are

NOTE Confidence: 0.846486428333333

00:23:12.721 --> 00:23:15.047 indicated for these different regions above.

NOTE Confidence: 0.846486428333333

00:23:15.050 --> 00:23:17.202 And so this is just to show how

NOTE Confidence: 0.846486428333333

00:23:17.202 --> 00:23:19.089 we could visualize the data.

NOTE Confidence: 0.846486428333333

00:23:19.090 --> 00:23:19.906 But of course,

NOTE Confidence: 0.846486428333333

00:23:19.906 --> 00:23:21.810 what we're really interested in are the

NOTE Confidence: 0.846486428333333

00:23:21.863 --> 00:23:23.879 quantifications that we derive for this.

NOTE Confidence: 0.846486428333333

00:23:23.880 --> 00:23:26.505 So coming back to the sort of

NOTE Confidence: 0.846486428333333

00:23:26.505 --> 00:23:27.630 baseline characteristics that

NOTE Confidence: 0.846486428333333

00:23:27.702 --> 00:23:29.550 I had shared with you before,

NOTE Confidence: 0.846486428333333

00:23:29.550 --> 00:23:32.392 we were now very interested in looking at

NOTE Confidence: 0.846486428333333

00:23:32.392 --> 00:23:34.989 two key markers starting with her two.

NOTE Confidence: 0.846486428333333

00:23:34.990 --> 00:23:36.908 Of course as well as CD 45.

NOTE Confidence: 0.846486428333333

00:23:36.910 --> 00:23:38.744 So these are the protein markers of

NOTE Confidence: 0.846486428333333

00:23:38.744 --> 00:23:40.793 interest you can see on the bottom

NOTE Confidence: 0.846486428333333

00:23:40.793 --> 00:23:42.303 that we've stratified by intrinsic

NOTE Confidence: 0.846486428333333

00:23:42.303 --> 00:23:44.296 subtype as well as ER status obviously

NOTE Confidence: 0.846486428333333

00:23:44.296 --> 00:23:45.633 critical to account for here,

NOTE Confidence: 0.846486428333333

00:23:45.633 --> 00:23:46.362 and Patsy R,

NOTE Confidence: 0.846486428333333

00:23:46.362 --> 00:23:48.186 and so each of these dots represents

NOTE Confidence: 0.846486428333333

00:23:48.186 --> 00:23:50.658 a not at the log 2 normalized digital

NOTE Confidence: 0.846486428333333

00:23:50.658 --> 00:23:52.408 spatial profiling protein levels.

NOTE Confidence: 0.846486428333333

00:23:52.410 --> 00:23:54.300 You can see that there is reasonably.

NOTE Confidence: 0.846486428333333

00:23:54.300 --> 00:23:54.860 You know,

NOTE Confidence: 0.846486428333333

00:23:54.860 --> 00:23:56.820 good clustering for some of these in

NOTE Confidence: 0.846486428333333

00:23:56.820 --> 00:23:58.638 terms of the levels of expression

NOTE Confidence: 0.846486428333333

00:23:58.638 --> 00:24:01.210 within a sample, but some cases also exhibit,

NOTE Confidence: 0.846486428333333

00:24:01.210 --> 00:24:03.990 you know, pretty considerable variability,

NOTE Confidence: 0.846486428333333

00:24:03.990 --> 00:24:06.610 and so this is if we want to look at

NOTE Confidence: 0.846486428333333

00:24:06.686 --> 00:24:08.337 each of the regions individually.

NOTE Confidence: 0.846486428333333

00:24:08.337 --> 00:24:09.672 And that's of course something

NOTE Confidence: 0.846486428333333

00:24:09.672 --> 00:24:11.289 we can do with these data.

NOTE Confidence: 0.846486428333333

00:24:11.290 --> 00:24:14.531 So this gives us a sense for

NOTE Confidence: 0.846486428333333

00:24:14.531 --> 00:24:15.920 the heterogeneity present.

NOTE Confidence: 0.846486428333333

00:24:15.920 --> 00:24:17.012 In these markers,

NOTE Confidence: 0.846486428333333

00:24:17.012 --> 00:24:19.196 and neither were predictive at baseline,

NOTE Confidence: 0.846486428333333

00:24:19.200 --> 00:24:21.448 neither of these protein

NOTE Confidence: 0.846486428333333

00:24:21.448 --> 00:24:23.202 markers were predictive of PCR.

NOTE Confidence: 0.846486428333333

00:24:23.202 --> 00:24:24.940 We can also, of course,

NOTE Confidence: 0.846486428333333

00:24:24.940 --> 00:24:27.040 look at her two heterogeneity

NOTE Confidence: 0.846486428333333

00:24:27.040 --> 00:24:29.260 with far greater granularity,

NOTE Confidence: 0.846486428333333

00:24:29.260 --> 00:24:31.716 and so one of the ways that you

NOTE Confidence: 0.846486428333333

00:24:31.716 --> 00:24:33.340 could envision doing this is,

NOTE Confidence: 0.846486428333333

00:24:33.340 --> 00:24:34.432 as we've represented here,

NOTE Confidence: 0.846486428333333

00:24:34.432 --> 00:24:36.070 taking the PCR cases and non

NOTE Confidence: 0.846486428333333

00:24:36.126 --> 00:24:37.316 PCR cases on the bottom.

NOTE Confidence: 0.846486428333333

00:24:37.320 --> 00:24:40.678 This is again for each each individual

NOTE Confidence: 0.846486428333333

00:24:40.678 --> 00:24:43.792 region or summarizing the her two

NOTE Confidence: 0.846486428333333

00:24:43.792 --> 00:24:46.208 protein levels and you can see.

NOTE Confidence: 0.846486428333333

00:24:46.210 --> 00:24:48.658 How they look pretreatment

NOTE Confidence: 0.846486428333333

00:24:48.658 --> 00:24:49.946 versus on treatment.

NOTE Confidence: 0.846486428333333

00:24:49.946 --> 00:24:50.622 Whenever available,

NOTE Confidence: 0.846486428333333

00:24:50.622 --> 00:24:53.287 you can see that there's quite a bit

NOTE Confidence: 0.846486428333333

00:24:53.287 --> 00:24:54.742 more variability in the on treatment,

NOTE Confidence: 0.846486428333333

00:24:54.742 --> 00:24:55.396 her two levels,

NOTE Confidence: 0.846486428333333

00:24:55.400 --> 00:24:57.480 and actually we quantified this.

NOTE Confidence: 0.846486428333333

00:24:57.480 --> 00:25:00.640 You can look at the mean square error

NOTE Confidence: 0.846486428333333

00:25:00.640 --> 00:25:02.555 within patients versus between patients

NOTE Confidence: 0.846486428333333

00:25:02.555 --> 00:25:05.260 and see that they're far more comparable.

NOTE Confidence: 0.846486428333333

00:25:05.260 --> 00:25:06.860 Pretreatment versus on treatment.

NOTE Confidence: 0.846486428333333

00:25:06.860 --> 00:25:07.654 I mean,

NOTE Confidence: 0.846486428333333

00:25:07.654 --> 00:25:10.433 we really have a quite dramatic degree

NOTE Confidence: 0.846486428333333

00:25:10.433 --> 00:25:13.510 of change in her two heterogeneity,

NOTE Confidence: 0.846486428333333

00:25:13.510 --> 00:25:15.508 and so this this tells us

NOTE Confidence: 0.846486428333333

00:25:15.508 --> 00:25:16.840 something of course about.

NOTE Confidence: 0.846486428333333

00:25:16.840 --> 00:25:18.540 You know both that were

NOTE Confidence: 0.846486428333333

00:25:18.540 --> 00:25:19.900 likely hitting the target,

NOTE Confidence: 0.846486428333333

00:25:19.900 --> 00:25:21.040 but what that you know?

NOTE Confidence: 0.846486428333333

00:25:21.040 --> 00:25:23.530 How do we interpret the functional

NOTE Confidence: 0.846486428333333

00:25:23.530 --> 00:25:25.190 importance of this heterogeneity

NOTE Confidence: 0.846486428333333

00:25:25.190 --> 00:25:26.954 so you know the beauty of the

NOTE Confidence: 0.846486428333333

00:25:26.954 --> 00:25:28.532 multiplexing here is that it's not

NOTE Confidence: 0.846486428333333

00:25:28.532 --> 00:25:30.074 just her two that's of interest,

NOTE Confidence: 0.846486428333333

00:25:30.080 --> 00:25:31.628 but we can actually do these

NOTE Confidence: 0.846486428333333

00:25:31.628 --> 00:25:33.585 kinds of analysis for all of the

NOTE Confidence: 0.846486428333333

00:25:33.585 --> 00:25:34.737 markers that we've profiled.

NOTE Confidence: 0.846486428333333

00:25:34.740 --> 00:25:37.260 And so this is just stratifying

NOTE Confidence: 0.846486428333333

00:25:37.260 --> 00:25:39.040 by pretreatment on treatment,

NOTE Confidence: 0.846486428333333

00:25:39.040 --> 00:25:42.400 looking at all two all tumor markers.

NOTE Confidence: 0.846486428333333

00:25:42.400 --> 00:25:43.348 Not surprisingly,

NOTE Confidence: 0.846486428333333

00:25:43.348 --> 00:25:46.666 the greatest change in her two heterogeneity.

NOTE Confidence: 0.846486428333333

00:25:46.670 --> 00:25:48.608 Is in heterogeneous for her too,

NOTE Confidence: 0.846486428333333

00:25:48.610 --> 00:25:50.969 but this is followed by Phospho S6.

NOTE Confidence: 0.846486428333333

00:25:50.970 --> 00:25:53.386 If we instead look at the immune markers,

NOTE Confidence: 0.846486428333333

00:25:53.390 --> 00:25:55.676 we see that the change is

NOTE Confidence: 0.846486428333333

00:25:55.676 --> 00:25:57.200 overall relatively less compared

NOTE Confidence: 0.912260702857143

00:25:57.269 --> 00:25:58.649 to the tumor markers,

NOTE Confidence: 0.912260702857143

00:25:58.650 --> 00:26:00.932 but amongst the top markers we do

NOTE Confidence: 0.912260702857143

00:26:00.932 --> 00:26:04.470 see differences in our CD3 and CD8.

NOTE Confidence: 0.912260702857143

00:26:04.470 --> 00:26:06.142 And I should emphasize right now that all

NOTE Confidence: 0.912260702857143

00:26:06.142 --> 00:26:08.068 of the data that I'm showing you at this

NOTE Confidence: 0.912260702857143

00:26:08.068 --> 00:26:09.873 point is based on the pan cytokeratin

NOTE Confidence: 0.912260702857143

00:26:09.873 --> 00:26:11.650 enriched regions and focusing in on those.

NOTE Confidence: 0.912260702857143

00:26:11.650 --> 00:26:14.070 So similarly we can ask, well, you know,

NOTE Confidence: 0.912260702857143

00:26:14.070 --> 00:26:16.212 how do these markers change or differ?

NOTE Confidence: 0.912260702857143

00:26:16.212 --> 00:26:18.459 Or is there any association between patients

NOTE Confidence: 0.912260702857143

00:26:18.459 --> 00:26:20.866 that achieve a PCR versus those that don't?

NOTE Confidence: 0.912260702857143

00:26:20.870 --> 00:26:22.998 And this is now beginning to compare

NOTE Confidence: 0.912260702857143

00:26:22.998 --> 00:26:25.028 these on treatment values and and you

NOTE Confidence: 0.912260702857143

00:26:25.028 --> 00:26:27.135 can see that there are indeed pretty

NOTE Confidence: 0.912260702857143

00:26:27.135 --> 00:26:28.959 dramatic differences between responders

NOTE Confidence: 0.912260702857143

00:26:28.959 --> 00:26:30.327 and non responders.

NOTE Confidence: 0.912260702857143

00:26:30.330 --> 00:26:31.926 So this is all very well.

NOTE Confidence: 0.912260702857143

00:26:31.930 --> 00:26:33.210 I want to come back to say that

NOTE Confidence: 0.912260702857143

00:26:33.210 --> 00:26:34.238 of course you know we were.

NOTE Confidence: 0.912260702857143

00:26:34.240 --> 00:26:35.280 Being fairly pragmatic in

NOTE Confidence: 0.912260702857143

00:26:35.280 --> 00:26:36.320 our initial approach here,

NOTE Confidence: 0.912260702857143

00:26:36.320 --> 00:26:37.204 asking well can we.

NOTE Confidence: 0.912260702857143

00:26:37.204 --> 00:26:38.530 What can we learn from these

NOTE Confidence: 0.912260702857143

00:26:38.578 --> 00:26:39.499 samples at baseline?

NOTE Confidence: 0.912260702857143

00:26:39.500 --> 00:26:42.084 It would be ideal if we had strong

NOTE Confidence: 0.912260702857143

00:26:42.084 --> 00:26:44.220 predictors of response at baseline,

NOTE Confidence: 0.912260702857143

00:26:44.220 --> 00:26:46.916 so this is just showing you the CD

NOTE Confidence: 0.912260702857143

00:26:46.916 --> 00:26:48.977 45 pretreatment levels in a vial

NOTE Confidence: 0.912260702857143

00:26:48.977 --> 00:26:50.957 implant for the PCR cases versus

NOTE Confidence: 0.912260702857143

00:26:51.027 --> 00:26:53.268 non PCR as well As for CD 56 and

NOTE Confidence: 0.912260702857143

00:26:53.268 --> 00:26:55.164 what you can hopefully appreciate

NOTE Confidence: 0.912260702857143

00:26:55.164 --> 00:26:57.630 based on these violins are that

NOTE Confidence: 0.912260702857143

00:26:57.701 --> 00:27:01.918 there's really very no association

NOTE Confidence: 0.912260702857143

00:27:01.920 --> 00:27:03.920 in in the pretreatment markers,

NOTE Confidence: 0.912260702857143

00:27:03.920 --> 00:27:04.856 but once we start to look.

NOTE Confidence: 0.912260702857143

00:27:04.860 --> 00:27:05.536 On treatment,

NOTE Confidence: 0.912260702857143

00:27:05.536 --> 00:27:07.226 we're actually starting to see

NOTE Confidence: 0.912260702857143

00:27:07.226 --> 00:27:08.822 that there are significant

NOTE Confidence: 0.912260702857143

00:27:08.822 --> 00:27:10.886 differences between these markers

NOTE Confidence: 0.912260702857143

00:27:10.890 --> 00:27:12.850 in the PCR versus non PCR cases.

NOTE Confidence: 0.912260702857143

00:27:12.850 --> 00:27:13.830 So that gave us some,

NOTE Confidence: 0.912260702857143

00:27:13.830 --> 00:27:14.452 you know,

NOTE Confidence: 0.912260702857143

00:27:14.452 --> 00:27:16.318 sort of encouragement just in from

NOTE Confidence: 0.912260702857143

00:27:16.318 --> 00:27:18.140 a univariate analysis perspective.

NOTE Confidence: 0.912260702857143

00:27:18.140 --> 00:27:21.500 But what really got us excited?

NOTE Confidence: 0.912260702857143

00:27:21.500 --> 00:27:23.999 Was when we started to look at

NOTE Confidence: 0.912260702857143

00:27:23.999 --> 00:27:26.295 these markers in concert and So

NOTE Confidence: 0.912260702857143

00:27:26.295 --> 00:27:30.610 what I'm showing you here in this.

NOTE Confidence: 0.912260702857143

00:27:30.610 --> 00:27:33.322 It plot is that we're looking at the

NOTE Confidence: 0.912260702857143

00:27:33.322 --> 00:27:35.342 significance or the negative log 10

NOTE Confidence: 0.912260702857143

00:27:35.342 --> 00:27:37.666 FDR adjusted P value from the change

NOTE Confidence: 0.912260702857143

00:27:37.666 --> 00:27:40.386 from run into baseline again in the pan,

NOTE Confidence: 0.912260702857143

00:27:40.390 --> 00:27:42.588 CK enriched regions and so now you

NOTE Confidence: 0.912260702857143

00:27:42.588 --> 00:27:45.324 can look at the PCR cases and see that

NOTE Confidence: 0.912260702857143

00:27:45.324 --> 00:27:47.770 a whole host of markers are lower,

NOTE Confidence: 0.912260702857143

00:27:47.770 --> 00:27:50.350 quite dramatically lower at running.

NOTE Confidence: 0.912260702857143

00:27:50.350 --> 00:27:52.498 These include her two but also

NOTE Confidence: 0.912260702857143

00:27:52.498 --> 00:27:54.489 phospho 6 phospho Akt Chi 67,

NOTE Confidence: 0.912260702857143

00:27:54.490 --> 00:27:56.710 phospho, Erk and so forth.

NOTE Confidence: 0.912260702857143

00:27:56.710 --> 00:28:00.742 So really the whole ham pathway.

NOTE Confidence: 0.912260702857143

00:28:00.742 --> 00:28:03.286 Is showing a decrease?

NOTE Confidence: 0.912260702857143

00:28:03.290 --> 00:28:05.528 On treatment in patients that respond,

NOTE Confidence: 0.912260702857143

00:28:05.530 --> 00:28:07.195 there is a concomitant increase

NOTE Confidence: 0.912260702857143

00:28:07.195 --> 00:28:09.430 in a number of immune markers,

NOTE Confidence: 0.912260702857143

00:28:09.430 --> 00:28:12.190 including CD45, CD, eight others,

NOTE Confidence: 0.912260702857143

00:28:12.190 --> 00:28:14.950 really quite dramatic opposition here,

NOTE Confidence: 0.912260702857143

00:28:14.950 --> 00:28:15.982 and in contrast,

NOTE Confidence: 0.912260702857143

00:28:15.982 --> 00:28:18.046 we did not observe these patterns

NOTE Confidence: 0.912260702857143

00:28:18.046 --> 00:28:19.628 in the non PCR cases,

NOTE Confidence: 0.912260702857143

00:28:19.630 --> 00:28:22.234 so you can see that a handful of

NOTE Confidence: 0.912260702857143

00:28:22.234 --> 00:28:24.124 these markers are indeed achieved.

NOTE Confidence: 0.912260702857143

00:28:24.130 --> 00:28:26.830 Significance based on the FDR and there is a,

NOTE Confidence: 0.912260702857143

00:28:26.830 --> 00:28:30.470 you know, sort of a modest log 2 fold change,

NOTE Confidence: 0.912260702857143

00:28:30.470 --> 00:28:32.522 but it is much attenuated relative

NOTE Confidence: 0.912260702857143

00:28:32.522 --> 00:28:33.890 to the PCR cases,

NOTE Confidence: 0.912260702857143

00:28:33.890 --> 00:28:34.940 so this was the 1st.

NOTE Confidence: 0.912260702857143

00:28:34.940 --> 00:28:37.334 Sign that we had some signal and

NOTE Confidence: 0.912260702857143

00:28:37.334 --> 00:28:40.549 these data and was really quite encouraging.

NOTE Confidence: 0.912260702857143

00:28:40.550 --> 00:28:42.630 Now I wanted to come back to the

NOTE Confidence: 0.912260702857143

00:28:42.630 --> 00:28:44.584 RNA seek data RNA data that I

NOTE Confidence: 0.912260702857143

00:28:44.584 --> 00:28:46.650 showed you in the very beginning,

NOTE Confidence: 0.912260702857143

00:28:46.650 --> 00:28:49.350 and to say that we took the match samples.

NOTE Confidence: 0.912260702857143

00:28:49.350 --> 00:28:51.020 So just subsetting the larger

NOTE Confidence: 0.912260702857143

00:28:51.020 --> 00:28:52.690 RNA fresh frozen cohort where

NOTE Confidence: 0.905109314666667

00:28:52.756 --> 00:28:54.592 we failed to observe an association

NOTE Confidence: 0.905109314666667

00:28:54.592 --> 00:28:56.662 and asking what if we take these

NOTE Confidence: 0.905109314666667

00:28:56.662 --> 00:28:58.228 markers and just look at the

NOTE Confidence: 0.905109314666667

00:28:58.228 --> 00:29:00.410 RNA level and what you can see.

NOTE Confidence: 0.905109314666667

00:29:00.410 --> 00:29:03.308 Is that really we see no signal

NOTE Confidence: 0.905109314666667

00:29:03.308 --> 00:29:05.790 here now this of course could

NOTE Confidence: 0.905109314666667

00:29:05.790 --> 00:29:07.390 be attributed to many factors.

NOTE Confidence: 0.905109314666667

00:29:07.390 --> 00:29:10.780 It could be due to admixture in the bulk RNA.

NOTE Confidence: 0.905109314666667

00:29:10.780 --> 00:29:12.844 It could be due to the fact that

NOTE Confidence: 0.905109314666667

00:29:12.844 --> 00:29:14.618 we've actually enriched for a pan

NOTE Confidence: 0.905109314666667

00:29:14.618 --> 00:29:16.113 set of keratin tumor enriched,

NOTE Confidence: 0.905109314666667

00:29:16.120 --> 00:29:19.060 you know, population using DSP.

NOTE Confidence: 0.905109314666667

00:29:19.060 --> 00:29:20.842 And thirdly, it could be due to the fact

NOTE Confidence: 0.905109314666667

00:29:20.842 --> 00:29:22.578 that you know protein is more proximal.

NOTE Confidence: 0.905109314666667

00:29:22.580 --> 00:29:23.680 Readout of these signaling pathway

NOTE Confidence: 0.905109314666667

00:29:23.680 --> 00:29:25.130 changes that we want to observe.

NOTE Confidence: 0.905109314666667

00:29:25.130 --> 00:29:27.170 So multiple factors here, of course,

NOTE Confidence: 0.905109314666667

00:29:27.170 --> 00:29:31.319 the ideal comparator would be to do DSP RNA.

NOTE Confidence: 0.905109314666667

00:29:31.320 --> 00:29:31.605 Unfortunately,

NOTE Confidence: 0.905109314666667

00:29:31.605 --> 00:29:33.600 when we did this at the time,

NOTE Confidence: 0.905109314666667

00:29:33.600 --> 00:29:36.093 the RNA probes, it was a 96 Plex panel.

NOTE Confidence: 0.905109314666667

00:29:36.100 --> 00:29:39.034 We did do it the signal to noise was.

NOTE Confidence: 0.905109314666667

00:29:39.040 --> 00:29:40.515 Incredibly poor and we really

NOTE Confidence: 0.905109314666667

00:29:40.515 --> 00:29:41.695 couldn't use those data,

NOTE Confidence: 0.905109314666667

00:29:41.700 --> 00:29:43.401 so it is an experiment that that

NOTE Confidence: 0.905109314666667

00:29:43.401 --> 00:29:45.321 I'm sort of curious about to get

NOTE Confidence: 0.905109314666667

00:29:45.321 --> 00:29:47.377 back to which of these factors is

NOTE Confidence: 0.905109314666667

00:29:47.377 --> 00:29:48.897 driving our observations and I'll

NOTE Confidence: 0.905109314666667

00:29:48.897 --> 00:29:51.932 speak a little bit more to that more,

NOTE Confidence: 0.905109314666667

00:29:51.932 --> 00:29:53.060 but but you know,

NOTE Confidence: 0.905109314666667

00:29:53.060 --> 00:29:55.868 I will place some bets on the fact

NOTE Confidence: 0.905109314666667

00:29:55.868 --> 00:29:58.658 that we are enriching for tumor,

NOTE Confidence: 0.905109314666667

00:29:58.660 --> 00:30:01.228 and we are reading this out of the

NOTE Confidence: 0.905109314666667

00:30:01.228 --> 00:30:03.190 protein level so encouraged by our

NOTE Confidence: 0.905109314666667

00:30:03.190 --> 00:30:05.410 the previous slide and showing that

NOTE Confidence: 0.905109314666667

00:30:05.410 --> 00:30:07.379 there was an association between

NOTE Confidence: 0.905109314666667

00:30:07.379 --> 00:30:09.294 multiple markers in the PCR.

NOTE Confidence: 0.905109314666667

00:30:09.300 --> 00:30:11.980 Cases we then went on to take the

NOTE Confidence: 0.905109314666667

00:30:11.980 --> 00:30:14.208 logical next step which was to

NOTE Confidence: 0.905109314666667

00:30:14.208 --> 00:30:16.434 ask could we develop a classifier

NOTE Confidence: 0.905109314666667

00:30:16.440 --> 00:30:18.812 in our discovery cohort?

NOTE Confidence: 0.905109314666667

00:30:18.812 --> 00:30:22.182 Our very small discovery cohort and

NOTE Confidence: 0.905109314666667

00:30:22.182 --> 00:30:24.192 ask whether we could potentially

NOTE Confidence: 0.905109314666667

00:30:24.192 --> 00:30:26.819 predict response and so this is an L2

NOTE Confidence: 0.905109314666667

00:30:26.819 --> 00:30:28.152 regularized regression model because

NOTE Confidence: 0.905109314666667

00:30:28.152 --> 00:30:30.090 we were really trying to understand

NOTE Confidence: 0.905109314666667

00:30:30.090 --> 00:30:31.879 what these data could tell us.

NOTE Confidence: 0.905109314666667

00:30:31.880 --> 00:30:35.205 What we have done is to look at the

NOTE Confidence: 0.905109314666667

00:30:35.205 --> 00:30:37.025 DSP markers combined ingredients.

NOTE Confidence: 0.905109314666667

00:30:37.030 --> 00:30:39.370 So this is an and.

NOTE Confidence: 0.905109314666667

00:30:39.370 --> 00:30:39.706 Yep,

NOTE Confidence: 0.905109314666667

00:30:39.706 --> 00:30:41.722 pre and on treatment and we're

NOTE Confidence: 0.905109314666667

00:30:41.722 --> 00:30:43.946 comparing this with the sort of classic

NOTE Confidence: 0.905109314666667

00:30:43.946 --> 00:30:46.470 markers that we have in the field today.

NOTE Confidence: 0.905109314666667

00:30:46.470 --> 00:30:48.650 Which is estrogen receptor status,

NOTE Confidence: 0.905109314666667

00:30:48.650 --> 00:30:50.684 which we know is associated with PCR in the

NOTE Confidence: 0.905109314666667

00:30:50.684 --> 00:30:52.688 her two positive setting as well as Pam.

NOTE Confidence: 0.905109314666667

00:30:52.690 --> 00:30:54.482 50 You can see that this is this

NOTE Confidence: 0.905109314666667

00:30:54.482 --> 00:30:55.972 purple line with amine OC of .5

NOTE Confidence: 0.905109314666667

00:30:55.972 --> 00:30:57.629 so not telling us a whole bunch.

NOTE Confidence: 0.905109314666667

00:30:57.630 --> 00:31:00.376 We also try to combine these and

NOTE Confidence: 0.905109314666667

00:31:00.376 --> 00:31:02.224 ask whether this would improve our

NOTE Confidence: 0.905109314666667

00:31:02.224 --> 00:31:04.386 prediction and answer is no but but

NOTE Confidence: 0.905109314666667

00:31:04.386 --> 00:31:06.526 we were reasonably encouraged by

NOTE Confidence: 0.905109314666667

00:31:06.526 --> 00:31:10.074 this AUC of .733. Obviously this is.

NOTE Confidence: 0.905109314666667

00:31:10.074 --> 00:31:13.615 In, you know, in the discovery cohort alone,

NOTE Confidence: 0.905109314666667

00:31:13.620 --> 00:31:17.295 using cross validation and so you know,

NOTE Confidence: 0.905109314666667

00:31:17.300 --> 00:31:18.917 encouraged by this the next question was,

NOTE Confidence: 0.905109314666667

00:31:18.920 --> 00:31:19.604 well, OK,

NOTE Confidence: 0.905109314666667

00:31:19.604 --> 00:31:21.656 what markers are actually informative here,

NOTE Confidence: 0.905109314666667

00:31:21.660 --> 00:31:24.306 and so looking at the marker coefficients

NOTE Confidence: 0.905109314666667

00:31:24.306 --> 00:31:26.419 with this within this L2 model,

NOTE Confidence: 0.905109314666667

00:31:26.420 --> 00:31:28.989 what we noticed was that really CD

NOTE Confidence: 0.905109314666667

00:31:28.989 --> 00:31:31.384 45 and adjacent to this the next

NOTE Confidence: 0.905109314666667

00:31:31.384 --> 00:31:34.166 one up was Vista were amongst the

NOTE Confidence: 0.905109314666667

00:31:34.166 --> 00:31:36.254 the largest marker coefficient,

NOTE Confidence: 0.905109314666667

00:31:36.260 --> 00:31:37.905 so that gave us some clues and

NOTE Confidence: 0.905109314666667

00:31:37.905 --> 00:31:39.619 this was in the on treatment.

NOTE Confidence: 0.905109314666667

00:31:39.620 --> 00:31:40.096 Right,

NOTE Confidence: 0.905109314666667

00:31:40.096 --> 00:31:42.952 shown here in pink in the

NOTE Confidence: 0.905109314666667

00:31:42.952 --> 00:31:44.380 on treatment biopsy.

NOTE Confidence: 0.931155261111111

00:31:44.380 --> 00:31:46.414 So with this in hand we then you know,

NOTE Confidence: 0.931155261111111

00:31:46.420 --> 00:31:48.300 got a bit bolder and said, well, OK.

NOTE Confidence: 0.931155261111111

00:31:48.300 --> 00:31:51.632 What if we just look at CD 45 DSP alone?

NOTE Confidence: 0.931155261111111

00:31:51.632 --> 00:31:53.390 I mean, this would obviously be a

NOTE Confidence: 0.931155261111111

00:31:53.390 --> 00:31:55.040 simpler way to approach this problem,

NOTE Confidence: 0.931155261111111

00:31:55.040 --> 00:31:56.745 and the answer was that

NOTE Confidence: 0.931155261111111

00:31:56.745 --> 00:31:58.032 in our discovery cohort,

NOTE Confidence: 0.931155261111111

00:31:58.032 --> 00:31:59.838 so this is using cross validation.

NOTE Confidence: 0.931155261111111

00:31:59.840 --> 00:32:02.598 We got a very very high AUC,

NOTE Confidence: 0.931155261111111

00:32:02.600 --> 00:32:05.453 almost too good to be true of .9 and

NOTE Confidence: 0.931155261111111

00:32:05.453 --> 00:32:08.784 so then we actually took this into our,

NOTE Confidence: 0.931155261111111

00:32:08.790 --> 00:32:11.106 you know, withheld validation set where

NOTE Confidence: 0.931155261111111

00:32:11.106 --> 00:32:13.700 we assess this in the AC was .75.

NOTE Confidence: 0.931155261111111

00:32:13.700 --> 00:32:14.900 So not too bad.

NOTE Confidence: 0.931155261111111

00:32:14.900 --> 00:32:16.220 Still encouraging enough and and this

NOTE Confidence: 0.931155261111111

00:32:16.220 --> 00:32:18.078 LED us to then kind of come back to

NOTE Confidence: 0.931155261111111

00:32:18.078 --> 00:32:19.480 what I mentioned at the beginning,

NOTE Confidence: 0.931155261111111

00:32:19.480 --> 00:32:21.736 which was what we had on treatment pills.

NOTE Confidence: 0.931155261111111

00:32:21.740 --> 00:32:24.220 We had scored these for the entire cohort.

NOTE Confidence: 0.931155261111111

00:32:24.220 --> 00:32:26.110 We hadn't seen an association at

NOTE Confidence: 0.931155261111111

00:32:26.110 --> 00:32:28.393 large with that and we had reported

NOTE Confidence: 0.931155261111111

00:32:28.393 --> 00:32:29.983 that along with the trial.

NOTE Confidence: 0.931155261111111

00:32:29.990 --> 00:32:31.673 But you know what are these trends look like?

NOTE Confidence: 0.931155261111111

00:32:31.680 --> 00:32:35.102 So so here you can see the on

NOTE Confidence: 0.931155261111111

00:32:35.102 --> 00:32:37.362 treatment tell score broken down

NOTE Confidence: 0.931155261111111

00:32:37.362 --> 00:32:40.512 by non PCR versus PCR and you know

NOTE Confidence: 0.931155261111111

00:32:40.512 --> 00:32:42.794 we really see a far more striking

NOTE Confidence: 0.931155261111111

00:32:42.794 --> 00:32:44.908 separation of PCR versus non PCR cases.

NOTE Confidence: 0.931155261111111

00:32:44.910 --> 00:32:47.297 Saying CD 45 DSP they are correlated

NOTE Confidence: 0.931155261111111

00:32:47.297 --> 00:32:50.068 but not as well as one would like.

NOTE Confidence: 0.931155261111111

00:32:50.070 --> 00:32:52.030 And that begs a number of questions

NOTE Confidence: 0.931155261111111

00:32:52.030 --> 00:32:54.601 and and of course it would be really

NOTE Confidence: 0.931155261111111

00:32:54.601 --> 00:32:56.640 interesting to ask you know why is that

NOTE Confidence: 0.931155261111111

00:32:56.640 --> 00:32:58.709 the case in in this PO7 clinical trial?

NOTE Confidence: 0.931155261111111

00:32:58.710 --> 00:33:01.190 And why have others seen more of an

NOTE Confidence: 0.931155261111111

00:33:01.190 --> 00:33:02.488 association? For example in Pamela?

NOTE Confidence: 0.931155261111111

00:33:02.488 --> 00:33:03.970 But as I showed you before,

NOTE Confidence: 0.931155261111111

00:33:03.970 --> 00:33:05.130 not this doesn't always validate,

NOTE Confidence: 0.931155261111111

00:33:05.130 --> 00:33:06.849 and I think you know it raises the question.

NOTE Confidence: 0.931155261111111

00:33:06.850 --> 00:33:09.910 There's of course a lot of inter and intra

NOTE Confidence: 0.931155261111111

00:33:09.910 --> 00:33:12.403 observer variability in scoring chills,

NOTE Confidence: 0.931155261111111

00:33:12.403 --> 00:33:15.560 and so perhaps that's a contributing factor.

NOTE Confidence: 0.931155261111111

00:33:15.560 --> 00:33:18.311 But so with this information in hand

NOTE Confidence: 0.931155261111111

00:33:18.311 --> 00:33:21.028 and encouraged by the fact that CD

NOTE Confidence: 0.931155261111111

00:33:21.028 --> 00:33:23.212 45 DSP protein alone on treatment

NOTE Confidence: 0.931155261111111

00:33:23.220 --> 00:33:26.776 seem to be predictive of a PCR,

NOTE Confidence: 0.931155261111111

00:33:26.780 --> 00:33:29.660 we then went on to really try to reduce

NOTE Confidence: 0.931155261111111

00:33:29.660 --> 00:33:32.897 this approach to a more simplistic strategy.

NOTE Confidence: 0.931155261111111

00:33:32.900 --> 00:33:35.460 And So what we did was to then

NOTE Confidence: 0.931155261111111

00:33:35.460 --> 00:33:37.270 come back and perform CD.

NOTE Confidence: 0.931155261111111

00:33:37.270 --> 00:33:39.820 45 I mean a histochemistry on

NOTE Confidence: 0.931155261111111

00:33:39.820 --> 00:33:41.978 the cohort we had in hand,

NOTE Confidence: 0.931155261111111

00:33:41.980 --> 00:33:44.080 and we gathered as many additional

NOTE Confidence: 0.931155261111111

00:33:44.080 --> 00:33:46.192 cases from this clinical trial which

NOTE Confidence: 0.931155261111111

00:33:46.192 --> 00:33:48.148 was near expended at this point.

NOTE Confidence: 0.931155261111111

00:33:48.150 --> 00:33:50.068 To use that as a validation set,

NOTE Confidence: 0.931155261111111

00:33:50.070 --> 00:33:51.645 and so importantly,

NOTE Confidence: 0.931155261111111

00:33:51.645 --> 00:33:56.050 we built into this an effort to enrich

NOTE Confidence: 0.931155261111111

00:33:56.050 --> 00:33:57.800 with expert pathology guidance for

NOTE Confidence: 0.931155261111111

00:33:57.800 --> 00:34:00.090 tumor for tumor and rich regions,

NOTE Confidence: 0.931155261111111

00:34:00.090 --> 00:34:02.211 and this was really trying to mimic

NOTE Confidence: 0.931155261111111

00:34:02.211 --> 00:34:04.897 what we had done with the pants

NOTE Confidence: 0.931155261111111

00:34:04.897 --> 00:34:06.605 cytokeratin enrichment using DSP.

NOTE Confidence: 0.931155261111111

00:34:06.610 --> 00:34:08.675 We then use Q path to really

NOTE Confidence: 0.931155261111111

00:34:08.675 --> 00:34:10.426 automate this process and develop

NOTE Confidence: 0.931155261111111

00:34:10.426 --> 00:34:12.038 a digital pathology workflow.

NOTE Confidence: 0.931155261111111

00:34:12.040 --> 00:34:13.270 So how does this look?

NOTE Confidence: 0.931155261111111

00:34:13.270 --> 00:34:16.070 Well, so now this is taking, you know,

NOTE Confidence: 0.931155261111111

00:34:16.070 --> 00:34:18.770 a comparison of the match cases where we had.

NOTE Confidence: 0.931155261111111

00:34:18.770 --> 00:34:21.135 And then CD 45 immunohistochemistry

NOTE Confidence: 0.931155261111111

00:34:21.135 --> 00:34:23.500 shown in orange versus those

NOTE Confidence: 0.931155261111111

00:34:23.578 --> 00:34:25.654 cases where we had CD 45 DSP.

NOTE Confidence: 0.931155261111111

00:34:25.654 --> 00:34:26.894 You can see that they're

NOTE Confidence: 0.931155261111111

00:34:26.894 --> 00:34:27.990 largely in agreement.

NOTE Confidence: 0.931155261111111

00:34:27.990 --> 00:34:30.610 The IHC does slightly better,

NOTE Confidence: 0.931155261111111

00:34:30.610 --> 00:34:33.770 but really these are very,

NOTE Confidence: 0.85091825

00:34:33.770 --> 00:34:35.204 you know, reasonable AUC's to observe

NOTE Confidence: 0.85091825

00:34:35.204 --> 00:34:36.928 and just to put this in context,

NOTE Confidence: 0.85091825

00:34:36.930 --> 00:34:38.652 then what we're what we really want

NOTE Confidence: 0.85091825

00:34:38.652 --> 00:34:40.467 to be able to do is ask, well,

NOTE Confidence: 0.85091825

00:34:40.467 --> 00:34:42.369 what is the positive predictive value?

NOTE Confidence: 0.85091825

00:34:42.370 --> 00:34:44.926 The chance that a tumor will

NOTE Confidence: 0.85091825

00:34:44.926 --> 00:34:46.630 have a pathologic complete

NOTE Confidence: 0.85091825

00:34:46.708 --> 00:34:48.568 response to TCLTCH or TCHL?

NOTE Confidence: 0.85091825

00:34:48.568 --> 00:34:51.284 So the three different arms in the study

NOTE Confidence: 0.85091825

00:34:51.284 --> 00:34:53.554 and we were able to then, you know,

NOTE Confidence: 0.85091825

00:34:53.554 --> 00:34:56.253 use this to sort of set a cut point and

NOTE Confidence: 0.85091825

00:34:56.253 --> 00:34:59.750 the positive predictive value for a CD.

NOTE Confidence: 0.85091825

00:34:59.750 --> 00:35:02.558 45% positivity greater than 20% is .82 here,

NOTE Confidence: 0.85091825

00:35:02.558 --> 00:35:05.050 and this is in this combined cohort.

NOTE Confidence: 0.85091825

00:35:05.050 --> 00:35:08.479 If we do this only in the validation set.

NOTE Confidence: 0.85091825

00:35:08.480 --> 00:35:09.600 Where we have fewer cases,

NOTE Confidence: 0.85091825

00:35:09.600 --> 00:35:11.740 it drops to about .71.

NOTE Confidence: 0.85091825

00:35:11.740 --> 00:35:12.764 But Needless to say,

NOTE Confidence: 0.85091825

00:35:12.764 --> 00:35:14.044 this was really encouraging and

NOTE Confidence: 0.85091825

00:35:14.044 --> 00:35:15.218 begs the question, you know,

NOTE Confidence: 0.85091825

00:35:15.218 --> 00:35:16.370 sort of just to come back to this,

NOTE Confidence: 0.85091825

00:35:16.370 --> 00:35:18.490 but we could go from a Multiplex assay

NOTE Confidence: 0.85091825

00:35:18.490 --> 00:35:20.323 and reduce this down to a single

NOTE Confidence: 0.85091825

00:35:20.323 --> 00:35:22.218 marker that could be run in any lab.

NOTE Confidence: 0.85091825

00:35:22.220 --> 00:35:24.397 We know that CD 45 is incredibly

NOTE Confidence: 0.85091825

00:35:24.397 --> 00:35:27.000 robust and raises the possibility that

NOTE Confidence: 0.85091825

00:35:27.000 --> 00:35:29.779 perhaps this kind of approach could

NOTE Confidence: 0.85091825

00:35:29.779 --> 00:35:32.670 be used to guide therapy D escalation.

NOTE Confidence: 0.85091825

00:35:32.670 --> 00:35:34.086 Now I'll come back to this.

NOTE Confidence: 0.85091825

00:35:34.090 --> 00:35:36.240 This will require further validation

NOTE Confidence: 0.85091825

00:35:36.240 --> 00:35:38.506 in additional trial cohorts, namely.

NOTE Confidence: 0.85091825

00:35:38.506 --> 00:35:41.782 Ideally those that did not administer

NOTE Confidence: 0.85091825

00:35:41.782 --> 00:35:42.328 chemotherapy.

NOTE Confidence: 0.85091825

00:35:42.330 --> 00:35:42.776 Afterwards,

NOTE Confidence: 0.85091825

00:35:42.776 --> 00:35:45.452 and we are actively now validating

NOTE Confidence: 0.85091825

00:35:45.452 --> 00:35:48.262 us in a in a retrospectively in

NOTE Confidence: 0.85091825

00:35:48.262 --> 00:35:50.102 one of those trial cohorts,

NOTE Confidence: 0.85091825

00:35:50.110 --> 00:35:52.630 and if that pans out then of course then

NOTE Confidence: 0.85091825

00:35:52.630 --> 00:35:55.215 next steps would be a prospective effort.

NOTE Confidence: 0.85091825

00:35:55.220 --> 00:35:57.550 So moving you know back,

NOTE Confidence: 0.85091825

00:35:57.550 --> 00:35:59.836 I just want to spend a few more minutes

NOTE Confidence: 0.85091825

00:35:59.836 --> 00:36:01.848 saying that we of course had much more

NOTE Confidence: 0.85091825

00:36:01.848 --> 00:36:04.068 data in this cohort that we could mine.

NOTE Confidence: 0.85091825

00:36:04.070 --> 00:36:06.723 We are very keen to really leverage

NOTE Confidence: 0.85091825

00:36:06.723 --> 00:36:09.547 what started out as a discovery effort,

NOTE Confidence: 0.85091825

00:36:09.550 --> 00:36:11.209 but LED us to this new biomarker.

NOTE Confidence: 0.85091825

00:36:11.210 --> 00:36:11.812 I mean,

NOTE Confidence: 0.85091825

00:36:11.812 --> 00:36:14.220 this really was a piloting of the technology.

NOTE Confidence: 0.85091825

00:36:14.220 --> 00:36:15.372 That uncovered some pretty

NOTE Confidence: 0.85091825

00:36:15.372 --> 00:36:16.236 interesting biology here,

NOTE Confidence: 0.85091825

00:36:16.240 --> 00:36:18.504 but sort of coming back to the data

NOTE Confidence: 0.85091825

00:36:18.504 --> 00:36:20.936 I showed you before that the non

NOTE Confidence: 0.85091825

00:36:20.936 --> 00:36:23.414 PCR cases really didn't show very

NOTE Confidence: 0.85091825

00:36:23.414 --> 00:36:25.514 dramatic changes at the pretreatment

NOTE Confidence: 0.85091825

00:36:25.514 --> 00:36:27.514 versus run in time point.

NOTE Confidence: 0.85091825

00:36:27.520 --> 00:36:27.852 However,

NOTE Confidence: 0.85091825

00:36:27.852 --> 00:36:30.176 if we take those same patients and

NOTE Confidence: 0.85091825

00:36:30.176 --> 00:36:32.684 now look at them at at the surgical

NOTE Confidence: 0.85091825

00:36:32.684 --> 00:36:34.196 versus pretreatment time points,

NOTE Confidence: 0.85091825

00:36:34.200 --> 00:36:35.999 so after they've completed the full course,

NOTE Confidence: 0.85091825

00:36:36.000 --> 00:36:38.947 what we see is actually that by

NOTE Confidence: 0.85091825

00:36:38.947 --> 00:36:41.752 then they do indeed exhibit a

NOTE Confidence: 0.85091825

00:36:41.752 --> 00:36:44.147 a reduction in her two.

NOTE Confidence: 0.85091825

00:36:44.150 --> 00:36:45.966 We'll see that there is a reduction in

NOTE Confidence: 0.85091825

00:36:45.966 --> 00:36:48.048 CHI 67 these other downstream markers,

NOTE Confidence: 0.85091825

00:36:48.050 --> 00:36:50.270 however, are less downregulated,

NOTE Confidence: 0.85091825

00:36:50.270 --> 00:36:52.490 and this potentially suggests

NOTE Confidence: 0.85091825

00:36:52.490 --> 00:36:54.870 compensatory signaling in the non PCR

NOTE Confidence: 0.85091825

00:36:54.870 --> 00:36:57.459 cases that's active at the time of surgery.

NOTE Confidence: 0.85091825

00:36:57.460 --> 00:36:59.323 I will point out as well that we do

NOTE Confidence: 0.85091825

00:36:59.323 --> 00:37:01.296 see shifts by the time of surgery

NOTE Confidence: 0.85091825

00:37:01.296 --> 00:37:03.464 in immune markers, including CD 56.

NOTE Confidence: 0.85091825

00:37:03.464 --> 00:37:06.530 And of course you know this raises

NOTE Confidence: 0.85091825

00:37:06.622 --> 00:37:07.740 the question.

NOTE Confidence: 0.85091825

00:37:07.740 --> 00:37:09.910 Why that might be the most enriches

NOTE Confidence: 0.85091825

00:37:09.910 --> 00:37:11.672 this because we're seeing an

NOTE Confidence: 0.85091825

00:37:11.672 --> 00:37:13.212 effective natural killer cells

NOTE Confidence: 0.85091825

00:37:13.212 --> 00:37:15.270 in identifying and killing these

NOTE Confidence: 0.85091825

00:37:15.270 --> 00:37:17.106 chemotherapy stressed tumor cells.

NOTE Confidence: 0.85091825

00:37:17.110 --> 00:37:19.980 You know that's that's possible.

NOTE Confidence: 0.85091825

00:37:19.980 --> 00:37:22.220 And so really a lot to unpack here,

NOTE Confidence: 0.85091825

00:37:22.220 --> 00:37:23.295 but I think it's quite

NOTE Confidence: 0.85091825

00:37:23.295 --> 00:37:24.370 interesting that now we do

NOTE Confidence: 0.961272315

00:37:24.418 --> 00:37:25.780 start to see these changes now.

NOTE Confidence: 0.961272315

00:37:25.780 --> 00:37:27.747 On top of this, I haven't really

NOTE Confidence: 0.961272315

00:37:27.747 --> 00:37:29.732 talked at all beyond what we can

NOTE Confidence: 0.961272315

00:37:29.732 --> 00:37:31.900 do with the tumor in rich regions.

NOTE Confidence: 0.961272315

00:37:31.900 --> 00:37:33.356 But as I mentioned in the beginning,

NOTE Confidence: 0.961272315

00:37:33.360 --> 00:37:35.502 you know a benefit of the DSP

NOTE Confidence: 0.961272315

00:37:35.502 --> 00:37:37.011 approach and the phenotypic

NOTE Confidence: 0.961272315

00:37:37.011 --> 00:37:39.616 selection strategy that we deployed.

NOTE Confidence: 0.961272315

00:37:39.620 --> 00:37:42.154 There are many others that one could

NOTE Confidence: 0.961272315

00:37:42.154 --> 00:37:45.565 envision is that we can now select the

NOTE Confidence: 0.961272315

00:37:45.565 --> 00:37:47.280 surrounding tumor microenvironment area,

NOTE Confidence: 0.961272315

00:37:47.280 --> 00:37:49.989 and so we wanted to explore that.

NOTE Confidence: 0.961272315

00:37:49.990 --> 00:37:51.850 You know a bit here,

NOTE Confidence: 0.961272315

00:37:51.850 --> 00:37:53.796 and So what I'm showing you is

NOTE Confidence: 0.961272315

00:37:53.796 --> 00:37:55.827 now looking at the enrichment of

NOTE Confidence: 0.961272315

00:37:55.827 --> 00:37:58.089 just immune genes in either the

NOTE Confidence: 0.961272315

00:37:58.089 --> 00:37:59.349 surrounding microenvironment that's

NOTE Confidence: 0.961272315

00:37:59.349 --> 00:38:01.803 shown over here on the right.

NOTE Confidence: 0.961272315

00:38:01.810 --> 00:38:04.785 So that's an enrichment towards the TME.

NOTE Confidence: 0.961272315

00:38:04.790 --> 00:38:07.823 The TME area versus in the tumor over here,

NOTE Confidence: 0.961272315

00:38:07.830 --> 00:38:10.318 and so this is in the first instance

NOTE Confidence: 0.961272315

00:38:10.318 --> 00:38:11.990 looking at the pretreatment time point

NOTE Confidence: 0.961272315

00:38:11.990 --> 00:38:14.134 where you can see is that there's really

NOTE Confidence: 0.961272315

00:38:14.134 --> 00:38:16.078 a number of immune suppressive marks

NOTE Confidence: 0.961272315

00:38:16.078 --> 00:38:18.290 evident in the tumor in rich region.

NOTE Confidence: 0.961272315

00:38:18.290 --> 00:38:20.390 We see evidence for T cell exclusion.

NOTE Confidence: 0.961272315

00:38:20.390 --> 00:38:22.070 Based on you know, CD3 CD,

NOTE Confidence: 0.961272315

00:38:22.070 --> 00:38:23.018 four other markers.

NOTE Confidence: 0.961272315

00:38:23.018 --> 00:38:25.230 I do want to be cautious here

NOTE Confidence: 0.961272315

00:38:25.302 --> 00:38:27.034 and why we sort of, you know,

NOTE Confidence: 0.961272315

00:38:27.034 --> 00:38:28.294 interpret this a little bit

NOTE Confidence: 0.961272315

00:38:28.294 --> 00:38:29.509 carefully is that you know,

NOTE Confidence: 0.961272315

00:38:29.510 --> 00:38:31.028 I think there's a lot of

NOTE Confidence: 0.961272315

00:38:31.028 --> 00:38:31.787 open questions around,

NOTE Confidence: 0.961272315

00:38:31.790 --> 00:38:32.855 just the relative.

NOTE Confidence: 0.961272315

00:38:32.855 --> 00:38:35.340 So we say stickiness affinity of these

NOTE Confidence: 0.961272315

00:38:35.409 --> 00:38:37.589 antibodies in tumor versus immune

NOTE Confidence: 0.961272315

00:38:37.589 --> 00:38:40.150 populations that we don't understand well,

NOTE Confidence: 0.961272315

00:38:40.150 --> 00:38:42.846 and that will need to be parsed further.

NOTE Confidence: 0.961272315

00:38:42.850 --> 00:38:43.750 And I say that in part,

NOTE Confidence: 0.961272315

00:38:43.750 --> 00:38:46.298 just noting that we see very, you know,

NOTE Confidence: 0.961272315

00:38:46.298 --> 00:38:48.290 high enrichment of B7H4 over here.

NOTE Confidence: 0.961272315

00:38:48.290 --> 00:38:50.788 So we could take that with a grain of salt,

NOTE Confidence: 0.961272315

00:38:50.790 --> 00:38:52.462 but of course what we can do is

NOTE Confidence: 0.961272315

00:38:52.462 --> 00:38:54.368 assume that those are going to be

NOTE Confidence: 0.961272315

00:38:54.368 --> 00:38:56.064 equivalent overtime and now ask well

NOTE Confidence: 0.961272315

00:38:56.064 --> 00:38:58.214 what happens in terms of these marks

NOTE Confidence: 0.961272315

00:38:58.214 --> 00:39:00.209 from pretreatment to on treatment,

NOTE Confidence: 0.961272315

00:39:00.210 --> 00:39:02.873 and you can see that you know really

NOTE Confidence: 0.961272315

00:39:02.873 --> 00:39:04.528 in the tumor enriched region,

NOTE Confidence: 0.961272315

00:39:04.530 --> 00:39:05.316 things stay large,

NOTE Confidence: 0.961272315

00:39:05.316 --> 00:39:07.490 largely the same at this first time point,

NOTE Confidence: 0.961272315

00:39:07.490 --> 00:39:09.434 by the time we get to the post

NOTE Confidence: 0.961272315

00:39:09.434 --> 00:39:10.300 treatment time point,

NOTE Confidence: 0.961272315

00:39:10.300 --> 00:39:13.594 we actually do see that you know many

NOTE Confidence: 0.961272315

00:39:13.594 --> 00:39:15.382 of these markers have now shifted.

NOTE Confidence: 0.961272315

00:39:15.390 --> 00:39:17.404 We see far less evidence of, you know,

NOTE Confidence: 0.961272315

00:39:17.404 --> 00:39:18.766 sort of this T cell exclusion.

NOTE Confidence: 0.961272315

00:39:18.770 --> 00:39:19.308 Now they've.

NOTE Confidence: 0.961272315

00:39:19.308 --> 00:39:20.922 Appeared to infiltrate and and I'll

NOTE Confidence: 0.961272315

00:39:20.922 --> 00:39:22.909 point out that this Last Post treatment,

NOTE Confidence: 0.961272315

00:39:22.910 --> 00:39:24.585 timepoint were of course only

NOTE Confidence: 0.961272315

00:39:24.585 --> 00:39:26.720 looking at the non PCR cases.

NOTE Confidence: 0.961272315

00:39:26.720 --> 00:39:29.261 We're not looking at the responders who

NOTE Confidence: 0.961272315

00:39:29.261 --> 00:39:31.688 presumably had no tumor cells present.

NOTE Confidence: 0.961272315

00:39:31.690 --> 00:39:31.974 Right,

NOTE Confidence: 0.961272315

00:39:31.974 --> 00:39:34.246 so this this gives us some clues as

NOTE Confidence: 0.961272315

00:39:34.246 --> 00:39:36.592 to also potentially the timing of

NOTE Confidence: 0.961272315

00:39:36.592 --> 00:39:38.582 changes of these immune markers,

NOTE Confidence: 0.961272315

00:39:38.590 --> 00:39:40.840 and you know raises the question

NOTE Confidence: 0.961272315

00:39:40.840 --> 00:39:43.125 as to whether further efforts to

NOTE Confidence: 0.961272315

00:39:43.125 --> 00:39:45.050 profile at multiple time points

NOTE Confidence: 0.961272315

00:39:45.050 --> 00:39:46.962 on therapy might actually inform

NOTE Confidence: 0.961272315

00:39:46.962 --> 00:39:49.110 you know the timing of these,

NOTE Confidence: 0.961272315

00:39:49.110 --> 00:39:51.618 I mean infiltrates and maybe have

NOTE Confidence: 0.961272315

00:39:51.618 --> 00:39:53.528 relevance for contemplating the timing

NOTE Confidence: 0.961272315

00:39:53.528 --> 00:39:55.308 of immunotherapy in these populations.

NOTE Confidence: 0.961272315

00:39:55.310 --> 00:39:57.155 And of course that will

NOTE Confidence: 0.961272315

00:39:57.155 --> 00:39:59.000 require further study as well.

NOTE Confidence: 0.961272315

00:39:59.000 --> 00:40:00.393 So I guess you know just to

NOTE Confidence: 0.961272315

00:40:00.393 --> 00:40:01.519 really wrap up this part.

NOTE Confidence: 0.961272315

00:40:01.520 --> 00:40:04.556 I'll say that Multiplex proteomic profiling,

NOTE Confidence: 0.961272315

00:40:04.560 --> 00:40:06.430 coupled with pan Cytokeratin and

NOTE Confidence: 0.961272315

00:40:06.430 --> 00:40:08.300 Richemond can reveal dynamic changes

NOTE Confidence: 0.838715517894737

00:40:08.357 --> 00:40:09.849 in the tumor microenvironment

NOTE Confidence: 0.838715517894737

00:40:09.849 --> 00:40:11.714 during her two targeted therapy.

NOTE Confidence: 0.838715517894737

00:40:11.720 --> 00:40:14.016 These data are data really under score the

NOTE Confidence: 0.838715517894737

00:40:14.016 --> 00:40:16.340 value of having a non treatment biopsy.

NOTE Confidence: 0.838715517894737

00:40:16.340 --> 00:40:18.804 That's obviously can be difficult to achieve,

NOTE Confidence: 0.838715517894737

00:40:18.810 --> 00:40:20.594 but this was instrumental.

NOTE Confidence: 0.838715517894737

00:40:20.594 --> 00:40:24.679 And really where we saw the most predictive.

NOTE Confidence: 0.838715517894737

00:40:24.680 --> 00:40:29.048 A potential of any of these biomarkers.

NOTE Confidence: 0.838715517894737

00:40:29.050 --> 00:40:31.130 We see that CD 45,

NOTE Confidence: 0.838715517894737

00:40:31.130 --> 00:40:34.175 either expression or cell counts as measured

NOTE Confidence: 0.838715517894737

00:40:34.175 --> 00:40:37.184 by HC predicted PCR in an independent

NOTE Confidence: 0.838715517894737

00:40:37.184 --> 00:40:39.620 set and this really did outperform

NOTE Confidence: 0.838715517894737

00:40:39.699 --> 00:40:42.051 other candidate biomarkers such as ER

NOTE Confidence: 0.838715517894737

00:40:42.051 --> 00:40:45.690 or her to enrich status and so we do.

NOTE Confidence: 0.838715517894737

00:40:45.690 --> 00:40:47.622 We think that these findings have

NOTE Confidence: 0.838715517894737

00:40:47.622 --> 00:40:48.910 implications for tailoring therapy.

NOTE Confidence: 0.838715517894737

00:40:48.910 --> 00:40:50.828 Of course, far more work is needed,

NOTE Confidence: 0.838715517894737

00:40:50.830 --> 00:40:53.245 but really the dream would be to

NOTE Confidence: 0.838715517894737

00:40:53.245 --> 00:40:56.207 be able to scare to spare patients

NOTE Confidence: 0.838715517894737

00:40:56.210 --> 00:40:59.730 who safely can omit chemotherapy.

NOTE Confidence: 0.838715517894737

00:40:59.730 --> 00:41:01.570 And to make that determination

NOTE Confidence: 0.838715517894737

00:41:01.570 --> 00:41:03.410 early during their treatment course

NOTE Confidence: 0.838715517894737

00:41:03.470 --> 00:41:05.522 and so this will require further

NOTE Confidence: 0.838715517894737

00:41:05.522 --> 00:41:06.599 validation which is ongoing.

NOTE Confidence: 0.838715517894737

00:41:06.599 --> 00:41:08.300 But I'll just say that you know,

NOTE Confidence: 0.838715517894737

00:41:08.300 --> 00:41:10.082 I think there's many other open

NOTE Confidence: 0.838715517894737

00:41:10.082 --> 00:41:11.575 questions that this work informs.

NOTE Confidence: 0.838715517894737

00:41:11.575 --> 00:41:12.185 Of course,

NOTE Confidence: 0.838715517894737

00:41:12.185 --> 00:41:14.660 you know it will be interesting to see

NOTE Confidence: 0.838715517894737

00:41:14.660 --> 00:41:16.916 how predictive CD 45 is in other cohorts,

NOTE Confidence: 0.838715517894737

00:41:16.920 --> 00:41:19.020 as well As for other anti

NOTE Confidence: 0.838715517894737

00:41:19.020 --> 00:41:20.420 her two targeted agents.

NOTE Confidence: 0.838715517894737

00:41:20.420 --> 00:41:22.364 I'm still very interested to better

NOTE Confidence: 0.838715517894737

00:41:22.364 --> 00:41:23.660 understand the comparison with

NOTE Confidence: 0.838715517894737

00:41:23.718 --> 00:41:25.524 cell till that hasn't really been

NOTE Confidence: 0.838715517894737

00:41:25.524 --> 00:41:26.692 head-to-head in larger cohorts.

NOTE Confidence: 0.838715517894737

00:41:26.692 --> 00:41:28.378 I think this raises the question

NOTE Confidence: 0.838715517894737

00:41:28.378 --> 00:41:30.039 about what is the optimal timing.

NOTE Confidence: 0.838715517894737

00:41:30.040 --> 00:41:32.259 We had this essentially one cycle of

NOTE Confidence: 0.838715517894737

00:41:32.259 --> 00:41:34.423 targeted therapy two week window because

NOTE Confidence: 0.838715517894737

00:41:34.423 --> 00:41:36.338 that's when patients were biopsied,

NOTE Confidence: 0.838715517894737

00:41:36.340 --> 00:41:37.825 and it's convenient.

NOTE Confidence: 0.838715517894737

00:41:37.825 --> 00:41:40.300 There may be better windows,

NOTE Confidence: 0.838715517894737

00:41:40.300 --> 00:41:42.000 but of course understanding this

NOTE Confidence: 0.838715517894737

00:41:42.000 --> 00:41:44.520 timing is going to be critical for

NOTE Confidence: 0.838715517894737

00:41:44.520 --> 00:41:46.408 really optimizing our interventions.

NOTE Confidence: 0.838715517894737

00:41:46.408 --> 00:41:48.768 And then there's many other

NOTE Confidence: 0.838715517894737

00:41:48.768 --> 00:41:50.580 questions about whether CD 45,

NOTE Confidence: 0.838715517894737

00:41:50.580 --> 00:41:53.408 you know will correlate with long term

NOTE Confidence: 0.838715517894737

00:41:53.408 --> 00:41:55.524 outcomes and whether its prognostic

NOTE Confidence: 0.838715517894737

00:41:55.524 --> 00:41:58.026 and or predictive in other subgroups

NOTE Confidence: 0.838715517894737

00:41:58.026 --> 00:42:00.649 of breast cancer and other cancers.

NOTE Confidence: 0.838715517894737

00:42:00.650 --> 00:42:03.082 So I'll say that you know there are

NOTE Confidence: 0.838715517894737

00:42:03.082 --> 00:42:05.322 many other efforts to contemplate

NOTE Confidence: 0.838715517894737

00:42:05.322 --> 00:42:06.879 D escalation strategies.

NOTE Confidence: 0.838715517894737

00:42:06.880 --> 00:42:11.216 One of these is the ADAPT trial,

NOTE Confidence: 0.838715517894737

00:42:11.216 --> 00:42:13.046 which is looking at neoadjuvant

NOTE Confidence: 0.838715517894737

00:42:13.046 --> 00:42:14.144 pertuzumab plus trustees.

NOTE Confidence: 0.838715517894737

00:42:14.150 --> 00:42:16.190 Mab with or without paclitaxel.

NOTE Confidence: 0.838715517894737

00:42:16.190 --> 00:42:19.110 Another trial is for gain,

NOTE Confidence: 0.838715517894737

00:42:19.110 --> 00:42:22.732 which is looking at and FDG PET based

NOTE Confidence: 0.838715517894737

00:42:22.732 --> 00:42:24.788 biomarker of Pathologic complete

NOTE Confidence: 0.838715517894737

00:42:24.788 --> 00:42:27.750 response and of course these are

NOTE Confidence: 0.838715517894737

00:42:27.750 --> 00:42:30.216 you know ongoing and reporting out.

NOTE Confidence: 0.838715517894737

00:42:30.220 --> 00:42:31.820 And really, just highlight,

NOTE Confidence: 0.838715517894737

00:42:31.820 --> 00:42:34.698 I think the the real efforts of

NOTE Confidence: 0.838715517894737

00:42:34.698 --> 00:42:37.098 the Community to try to identify

NOTE Confidence: 0.838715517894737

00:42:37.098 --> 00:42:39.506 these biomarkers and two to optimize

NOTE Confidence: 0.838715517894737

00:42:39.506 --> 00:42:40.880 for our patients.

NOTE Confidence: 0.838715517894737

00:42:40.880 --> 00:42:42.707 Now I will say that of course

NOTE Confidence: 0.838715517894737

00:42:42.707 --> 00:42:44.500 I've I've mentioned this in the

NOTE Confidence: 0.838715517894737

00:42:44.500 --> 00:42:45.457 context of deescalation.

NOTE Confidence: 0.838715517894737

00:42:45.460 --> 00:42:48.970 Really the flip side of that coin is that

NOTE Confidence: 0.838715517894737

00:42:48.970 --> 00:42:51.757 ultimately we're very likely to need risk.

NOTE Confidence: 0.838715517894737

00:42:51.760 --> 00:42:54.706 Adapted novel trial designs to tailor

NOTE Confidence: 0.838715517894737

00:42:54.706 --> 00:42:57.559 therapy and deliver new drugs to

NOTE Confidence: 0.838715517894737

00:42:57.559 --> 00:43:00.373 high risk patients as needed and so.

NOTE Confidence: 0.838715517894737

00:43:00.380 --> 00:43:01.634 We've been contemplating that a little

NOTE Confidence: 0.838715517894737

00:43:01.634 --> 00:43:03.344 bit more in the ER positive her two

NOTE Confidence: 0.838715517894737

00:43:03.344 --> 00:43:04.830 negative setting and I'll just say that,

NOTE Confidence: 0.838715517894737

00:43:04.830 --> 00:43:05.382 you know,

NOTE Confidence: 0.838715517894737

00:43:05.382 --> 00:43:07.314 sort of building on from this work

NOTE Confidence: 0.838715517894737

00:43:07.314 --> 00:43:09.334 we've now embarked on a number of

NOTE Confidence: 0.838715517894737

00:43:09.334 --> 00:43:11.680 other efforts to really chart not only

NOTE Confidence: 0.838715517894737

00:43:11.680 --> 00:43:13.224 the tumor immune microenvironment,

NOTE Confidence: 0.838715517894737

00:43:13.230 --> 00:43:15.034 but to characterize tumor

NOTE Confidence: 0.838715517894737

00:43:15.034 --> 00:43:16.387 evolution through therapy.

NOTE Confidence: 0.838715517894737

00:43:16.390 --> 00:43:18.064 And that's been on a really

NOTE Confidence: 0.838715517894737

00:43:18.064 --> 00:43:19.180 long standing interest in

NOTE Confidence: 0.940547038333333

00:43:19.240 --> 00:43:20.642 my lab. We are using a

NOTE Confidence: 0.940547038333333

00:43:20.642 --> 00:43:22.190 variety of tools to do this,

NOTE Confidence: 0.940547038333333

00:43:22.190 --> 00:43:24.450 not only spatial proteomics,

NOTE Confidence: 0.940547038333333

00:43:24.450 --> 00:43:26.145 but also transcriptomics,

NOTE Confidence: 0.940547038333333

00:43:26.150 --> 00:43:28.562 which you know affords us maybe

NOTE Confidence: 0.940547038333333

00:43:28.562 --> 00:43:30.448 a less biased approach, and.

NOTE Confidence: 0.940547038333333

00:43:30.448 --> 00:43:32.394 Enables discovery efforts and and for many

NOTE Confidence: 0.940547038333333

00:43:32.394 --> 00:43:34.497 of these cohorts that we're working on,

NOTE Confidence: 0.940547038333333

00:43:34.500 --> 00:43:36.885 we've previously performed end up

NOTE Confidence: 0.940547038333333

00:43:36.885 --> 00:43:40.110 sequencing mainly at the bulk DNA level,

NOTE Confidence: 0.940547038333333

00:43:40.110 --> 00:43:42.120 but in some cases when possible.

NOTE Confidence: 0.940547038333333

00:43:42.120 --> 00:43:44.028 We're also doing this, you know,

NOTE Confidence: 0.940547038333333

00:43:44.030 --> 00:43:45.030 at the single cell level,

NOTE Confidence: 0.940547038333333

00:43:45.030 --> 00:43:47.410 to try to tease apart this biology,

NOTE Confidence: 0.940547038333333

00:43:47.410 --> 00:43:49.909 and so one of the areas that

NOTE Confidence: 0.940547038333333

00:43:49.909 --> 00:43:51.230 we're particularly interested in,

NOTE Confidence: 0.940547038333333

00:43:51.230 --> 00:43:53.450 and that I'll just summarize

NOTE Confidence: 0.940547038333333

00:43:53.450 --> 00:43:55.670 briefly is in understanding the

NOTE Confidence: 0.940547038333333

00:43:55.745 --> 00:43:58.035 determinants of breast cancer relapse

NOTE Confidence: 0.940547038333333

00:43:58.035 --> 00:44:01.000 and so to highlight this problem.

NOTE Confidence: 0.940547038333333

00:44:01.000 --> 00:44:01.470 You know,

NOTE Confidence: 0.940547038333333

00:44:01.470 --> 00:44:02.880 I think we all appreciate that

NOTE Confidence: 0.940547038333333

00:44:02.880 --> 00:44:04.395 prognosis has improved dramatically for

NOTE Confidence: 0.940547038333333

00:44:04.395 --> 00:44:06.055 early stage breast cancer patients,

NOTE Confidence: 0.940547038333333

00:44:06.060 --> 00:44:08.316 in part due to new therapeutic

NOTE Confidence: 0.940547038333333

00:44:08.316 --> 00:44:09.820 strategies and screening and,

NOTE Confidence: 0.940547038333333

00:44:09.820 --> 00:44:11.143 and we certainly know this is the

NOTE Confidence: 0.940547038333333

00:44:11.143 --> 00:44:12.619 case for her two positive disease,

NOTE Confidence: 0.940547038333333

00:44:12.620 --> 00:44:14.738 but but for many other subgroups.

NOTE Confidence: 0.940547038333333

00:44:14.740 --> 00:44:16.756 And yet at the same time more

NOTE Confidence: 0.940547038333333

00:44:16.756 --> 00:44:19.204 than 20% of patients will recur

NOTE Confidence: 0.940547038333333

00:44:19.204 --> 00:44:21.534 with Mets at distant sites,

NOTE Confidence: 0.940547038333333

00:44:21.540 --> 00:44:23.960 and this remains largely incurable.

NOTE Confidence: 0.940547038333333

00:44:23.960 --> 00:44:26.720 There was a very powerful meta

NOTE Confidence: 0.940547038333333

00:44:26.720 --> 00:44:28.560 analysis performed by panel

NOTE Confidence: 0.940547038333333

00:44:28.639 --> 00:44:30.859 published several years ago.

NOTE Confidence: 0.940547038333333

00:44:30.860 --> 00:44:32.440 Which demonstrated that there's a

NOTE Confidence: 0.940547038333333

00:44:32.440 --> 00:44:34.550 subset of women with early stage ER,

NOTE Confidence: 0.940547038333333

00:44:34.550 --> 00:44:36.344 positive breast cancer who have a

NOTE Confidence: 0.940547038333333

00:44:36.344 --> 00:44:38.422 persistent risk of recurrence and death

NOTE Confidence: 0.940547038333333

00:44:38.422 --> 00:44:41.068 2 decades after their initial diagnosis,

NOTE Confidence: 0.940547038333333

00:44:41.070 --> 00:44:43.230 and these include women

NOTE Confidence: 0.940547038333333

00:44:43.230 --> 00:44:45.072 with node negative disease.

NOTE Confidence: 0.940547038333333

00:44:45.072 --> 00:44:47.676 As you can see over here,

NOTE Confidence: 0.940547038333333

00:44:47.680 --> 00:44:49.555 and so really illuminating what's

NOTE Confidence: 0.940547038333333

00:44:49.555 --> 00:44:51.430 been observed in clinical practice.

NOTE Confidence: 0.940547038333333

00:44:51.430 --> 00:44:51.770 Now,

NOTE Confidence: 0.940547038333333

00:44:51.770 --> 00:44:54.150 a key challenge of this has been

NOTE Confidence: 0.940547038333333

00:44:54.150 --> 00:44:56.810 that it's evident that our classic

NOTE Confidence: 0.940547038333333

00:44:56.810 --> 00:44:58.666 characteristics of nodal status,

NOTE Confidence: 0.940547038333333

00:44:58.670 --> 00:45:00.698 size, grade are insufficient.

NOTE Confidence: 0.940547038333333

00:45:00.698 --> 00:45:02.219 To predict recurrence,

NOTE Confidence: 0.940547038333333

00:45:02.220 --> 00:45:04.376 and really that the progress in the

NOTE Confidence: 0.940547038333333

00:45:04.376 --> 00:45:06.703 space has been impeded by the lack

NOTE Confidence: 0.940547038333333

00:45:06.703 --> 00:45:08.701 of cohorts with long term clinical

NOTE Confidence: 0.940547038333333

00:45:08.768 --> 00:45:10.560 follow-up and molecular data.

NOTE Confidence: 0.940547038333333

00:45:10.560 --> 00:45:14.576 And so this is really a segue to

NOTE Confidence: 0.940547038333333

00:45:14.580 --> 00:45:16.778 just a brief summary of of other

NOTE Confidence: 0.940547038333333

00:45:16.778 --> 00:45:18.873 work that we've been pursuing where

NOTE Confidence: 0.940547038333333

00:45:18.873 --> 00:45:21.393 several years ago now a decade ago.

NOTE Confidence: 0.940547038333333

00:45:21.400 --> 00:45:21.971 Actually,

NOTE Confidence: 0.940547038333333

00:45:21.971 --> 00:45:25.397 we sought to unpack the genomic

NOTE Confidence: 0.940547038333333

00:45:25.397 --> 00:45:27.860 landscape of breast cancer,

NOTE Confidence: 0.940547038333333

00:45:27.860 --> 00:45:30.335 really focusing on combining whole

NOTE Confidence: 0.940547038333333

00:45:30.335 --> 00:45:32.810 genome copy number based profiling.

NOTE Confidence: 0.940547038333333

00:45:32.810 --> 00:45:34.750 Quick transcriptomics and using

NOTE Confidence: 0.940547038333333

00:45:34.750 --> 00:45:36.690 unsupervised approaches we discovered

NOTE Confidence: 0.940547038333333

00:45:36.690 --> 00:45:39.090 that there are at least 10 molecularly

NOTE Confidence: 0.940547038333333

00:45:39.090 --> 00:45:40.930 distinct groups of disease.

NOTE Confidence: 0.940547038333333

00:45:40.930 --> 00:45:41.950 You can see these over here.

NOTE Confidence: 0.940547038333333

00:45:41.950 --> 00:45:44.596 This is the chromosome copy number

NOTE Confidence: 0.940547038333333

00:45:44.596 --> 00:45:46.360 in red shows amplifications,

NOTE Confidence: 0.940547038333333

00:45:46.360 --> 00:45:47.850 deletions in blue looking along

NOTE Confidence: 0.940547038333333

00:45:47.850 --> 00:45:48.446 the chromosome,

NOTE Confidence: 0.940547038333333

00:45:48.450 --> 00:45:50.388 and you'll recognize the Pam 50

NOTE Confidence: 0.940547038333333

00:45:50.388 --> 00:45:52.107 intrinsic subgroups and then our

NOTE Confidence: 0.940547038333333

00:45:52.107 --> 00:45:53.947 integrative subgroups on the outside.

NOTE Confidence: 0.940547038333333

00:45:53.950 --> 00:45:56.308 You can see that we really

NOTE Confidence: 0.940547038333333

00:45:56.310 --> 00:45:57.990 discover a number of groups.

NOTE Confidence: 0.940547038333333

00:45:57.990 --> 00:45:59.886 Not only do we recover, of course,

NOTE Confidence: 0.940547038333333

00:45:59.886 --> 00:46:01.590 the her two positive Group A great control,

NOTE Confidence: 0.940547038333333

00:46:01.590 --> 00:46:03.078 but we see other groups such

NOTE Confidence: 0.940547038333333

00:46:03.078 --> 00:46:03.822 as integrative cluster.

NOTE Confidence: 0.940547038333333

00:46:03.830 --> 00:46:05.348 One which has amplification of ARP,

NOTE Confidence: 0.940547038333333

00:46:05.350 --> 00:46:06.172 6 KB,

NOTE Confidence: 0.940547038333333

00:46:06.172 --> 00:46:09.104 one on chromosome 17 Q integrative cluster,

NOTE Confidence: 0.940547038333333

00:46:09.104 --> 00:46:09.978 6 amplification.

NOTE Confidence: 0.940547038333333

00:46:09.978 --> 00:46:11.289 Overexpression of FGFR,

NOTE Confidence: 0.940547038333333

00:46:11.290 --> 00:46:14.615 one on chromosome 8P12 and then this

NOTE Confidence: 0.940547038333333

00:46:14.615 --> 00:46:16.516 highly complex integrated cluster

NOTE Confidence: 0.940547038333333

00:46:16.516 --> 00:46:19.354 two with amplification of a cassette

NOTE Confidence: 0.940547038333333

00:46:19.354 --> 00:46:21.700 of chromatin regulators on 11 Q.

NOTE Confidence: 0.940547038333333

00:46:21.700 --> 00:46:23.610 So additional subgroups that are

NOTE Confidence: 0.940547038333333

00:46:23.610 --> 00:46:25.520 very much copy number defined

NOTE Confidence: 0.940547038333333

00:46:25.589 --> 00:46:27.962 and we were able to further show

NOTE Confidence: 0.940547038333333

00:46:27.962 --> 00:46:28.979 that these integrative

NOTE Confidence: 0.895192625769231

00:46:29.045 --> 00:46:30.557 subgroups really have

NOTE Confidence: 0.895192625769231

00:46:30.557 --> 00:46:32.069 distinct clinical outcomes.

NOTE Confidence: 0.895192625769231

00:46:32.070 --> 00:46:33.114 This is this cohort,

NOTE Confidence: 0.895192625769231

00:46:33.114 --> 00:46:34.680 obviously by virtue of the long

NOTE Confidence: 0.895192625769231

00:46:34.737 --> 00:46:36.699 follow-up predated the use of trustees,

NOTE Confidence: 0.895192625769231

00:46:36.700 --> 00:46:38.380 and Ave can see the integrative Cluster

NOTE Confidence: 0.895192625769231

00:46:38.380 --> 00:46:40.357 5 or her two positive group here,

NOTE Confidence: 0.895192625769231

00:46:40.360 --> 00:46:41.628 but numerous other groups

NOTE Confidence: 0.895192625769231

00:46:41.628 --> 00:46:42.896 have very steep trajectories.

NOTE Confidence: 0.895192625769231

00:46:42.900 --> 00:46:45.198 So just to recap what what

NOTE Confidence: 0.895192625769231

00:46:45.198 --> 00:46:47.915 this really told us is that in

NOTE Confidence: 0.895192625769231

00:46:47.915 --> 00:46:49.954 addition to the her two positive

NOTE Confidence: 0.895192625769231

00:46:49.954 --> 00:46:51.584 subgroup or integrated Cluster 5.

NOTE Confidence: 0.895192625769231

00:46:51.590 --> 00:46:53.022 Many other subgroups are

NOTE Confidence: 0.895192625769231

00:46:53.022 --> 00:46:54.454 copying overdriven and might

NOTE Confidence: 0.895192625769231

00:46:54.454 --> 00:46:56.090 share similar characteristics,

NOTE Confidence: 0.895192625769231

00:46:56.090 --> 00:46:58.323 and so in recent years we've been

NOTE Confidence: 0.895192625769231

00:46:58.323 --> 00:47:01.166 able to go back and obtain the 20

NOTE Confidence: 0.895192625769231

00:47:01.166 --> 00:47:03.513 year clinical follow up for this

NOTE Confidence: 0.895192625769231

00:47:03.513 --> 00:47:06.249 metabolic cohort of over 2000 patients,

NOTE Confidence: 0.895192625769231

00:47:06.250 --> 00:47:08.154 and So what I'm showing you here is

NOTE Confidence: 0.895192625769231

00:47:08.154 --> 00:47:10.446 just a summary broken down by ear

NOTE Confidence: 0.895192625769231

00:47:10.446 --> 00:47:12.201 positive and ear negative patients.

NOTE Confidence: 0.895192625769231

00:47:12.210 --> 00:47:13.510 Each patient along the vertical.

NOTE Confidence: 0.895192625769231

00:47:13.510 --> 00:47:15.708 You can see the site of metastasis

NOTE Confidence: 0.895192625769231

00:47:15.708 --> 00:47:16.650 for these patients.

NOTE Confidence: 0.895192625769231

00:47:16.650 --> 00:47:17.958 You can see that they're vast,

NOTE Confidence: 0.895192625769231

00:47:17.960 --> 00:47:21.936 so there's a huge degree of organic tropism.

NOTE Confidence: 0.895192625769231

00:47:21.940 --> 00:47:22.550 But really,

NOTE Confidence: 0.895192625769231

00:47:22.550 --> 00:47:24.075 what's critical about these data

NOTE Confidence: 0.895192625769231

00:47:24.075 --> 00:47:26.386 with long term follow up is that

NOTE Confidence: 0.895192625769231

00:47:26.386 --> 00:47:28.066 now having this complete recurrence

NOTE Confidence: 0.895192625769231

00:47:28.066 --> 00:47:29.487 information allows us to study

NOTE Confidence: 0.895192625769231

00:47:29.487 --> 00:47:31.035 the rates and routes of distant

NOTE Confidence: 0.895192625769231

00:47:31.040 --> 00:47:32.228 relapse and their lethality,

NOTE Confidence: 0.895192625769231

00:47:32.228 --> 00:47:34.699 and so I won't dwell on these data.

NOTE Confidence: 0.895192625769231

00:47:34.700 --> 00:47:37.200 They're all publicly available,

NOTE Confidence: 0.895192625769231

00:47:37.200 --> 00:47:39.520 but what this led us to is to then really

NOTE Confidence: 0.895192625769231

00:47:39.578 --> 00:47:41.298 revisit these integrative subgroups

NOTE Confidence: 0.895192625769231

00:47:41.298 --> 00:47:43.878 and their association with relapse risk,

NOTE Confidence: 0.895192625769231

00:47:43.880 --> 00:47:46.632 and So what I'm showing you here is

NOTE Confidence: 0.895192625769231

00:47:46.632 --> 00:47:48.635 the probability of relapse ordered

NOTE Confidence: 0.895192625769231

00:47:48.635 --> 00:47:51.460 by increasing risk for individuals.

NOTE Confidence: 0.895192625769231

00:47:51.460 --> 00:47:52.560 And I'll walk through starting

NOTE Confidence: 0.895192625769231

00:47:52.560 --> 00:47:53.440 with her two positive.

NOTE Confidence: 0.895192625769231

00:47:53.440 --> 00:47:53.717 Again,

NOTE Confidence: 0.895192625769231

00:47:53.717 --> 00:47:56.002 before the use of trustees met Ian Black,

NOTE Confidence: 0.895192625769231

00:47:56.002 --> 00:47:58.179 you can see after surgery there risks

NOTE Confidence: 0.895192625769231

00:47:58.179 --> 00:48:00.416 over this 20 year interval in red

NOTE Confidence: 0.895192625769231

00:48:00.416 --> 00:48:02.320 after being disease free five years

NOTE Confidence: 0.895192625769231

00:48:02.320 --> 00:48:04.420 and in green disease free 10 years.

NOTE Confidence: 0.895192625769231

00:48:04.420 --> 00:48:05.820 And of course these trajectories

NOTE Confidence: 0.895192625769231

00:48:05.820 --> 00:48:06.940 are are very steep.

NOTE Confidence: 0.895192625769231

00:48:06.940 --> 00:48:08.756 We know her too is a bad actor

NOTE Confidence: 0.895192625769231

00:48:08.756 --> 00:48:10.199 prior to trustees moving.

NOTE Confidence: 0.895192625769231

00:48:10.200 --> 00:48:11.580 This has changed the game,

NOTE Confidence: 0.895192625769231

00:48:11.580 --> 00:48:13.716 but we were intrigued to see that just

NOTE Confidence: 0.895192625769231

00:48:13.716 --> 00:48:15.669 adjacent to the her two positive group

NOTE Confidence: 0.895192625769231

00:48:15.669 --> 00:48:17.733 where these four what we term high

NOTE Confidence: 0.895192625769231

00:48:17.733 --> 00:48:19.980 risk ER positive her two negative subgroups,

NOTE Confidence: 0.895192625769231

00:48:19.980 --> 00:48:22.278 integrative clusters 169 and two which

NOTE Confidence: 0.895192625769231

00:48:22.278 --> 00:48:24.439 happened to be defined by those.

NOTE Confidence: 0.895192625769231

00:48:24.440 --> 00:48:25.466 Hallmark copying appropriations.

NOTE Confidence: 0.895192625769231

00:48:25.466 --> 00:48:26.834 I just showed you,

NOTE Confidence: 0.895192625769231

00:48:26.840 --> 00:48:27.791 and so really.

NOTE Confidence: 0.895192625769231

00:48:27.791 --> 00:48:29.693 Hopefully you can appreciate that the

NOTE Confidence: 0.895192625769231

00:48:29.693 --> 00:48:31.598 risks of relapse are in excess of,

NOTE Confidence: 0.895192625769231

00:48:31.600 --> 00:48:32.136 you know,

NOTE Confidence: 0.895192625769231

00:48:32.136 --> 00:48:35.308 in some cases 55% and this persists.

NOTE Confidence: 0.895192625769231

00:48:35.308 --> 00:48:37.348 Five 1020 years after diagnosis,

NOTE Confidence: 0.895192625769231

00:48:37.348 --> 00:48:39.981 so we believe that this subset of

NOTE Confidence: 0.895192625769231

00:48:39.981 --> 00:48:42.339 patients may correspond to the late

NOTE Confidence: 0.895192625769231

00:48:42.339 --> 00:48:44.239 relapsing groups defined by PAN

NOTE Confidence: 0.895192625769231

00:48:44.239 --> 00:48:46.189 at all for which biomarkers have

NOTE Confidence: 0.895192625769231

00:48:46.189 --> 00:48:47.844 been lacking now adjacent to this.

NOTE Confidence: 0.895192625769231

00:48:47.844 --> 00:48:49.099 There are two subgroups of

NOTE Confidence: 0.895192625769231

00:48:49.099 --> 00:48:50.180 triple negative disease,

NOTE Confidence: 0.895192625769231

00:48:50.180 --> 00:48:53.393 so I see 10 is a classic baselight group.

NOTE Confidence: 0.895192625769231

00:48:53.400 --> 00:48:54.793 You can see the risk of relapse

NOTE Confidence: 0.895192625769231

00:48:54.793 --> 00:48:55.670 plateaus after five years.

NOTE Confidence: 0.895192625769231

00:48:55.670 --> 00:48:56.978 Integrative cluster for this,

NOTE Confidence: 0.895192625769231

00:48:56.978 --> 00:48:58.613 ER negative group actually has

NOTE Confidence: 0.895192625769231

00:48:58.613 --> 00:49:00.369 a increased risk of relapse,

NOTE Confidence: 0.895192625769231

00:49:00.370 --> 00:49:02.278 which better mirrors the ER positive

NOTE Confidence: 0.895192625769231

00:49:02.278 --> 00:49:04.172 groups and they have dramatically

NOTE Confidence: 0.895192625769231

00:49:04.172 --> 00:49:06.310 different immune landscapes and then

NOTE Confidence: 0.895192625769231

00:49:06.310 --> 00:49:08.150 over here we have our more typical risk.

NOTE Confidence: 0.895192625769231

00:49:08.150 --> 00:49:10.496 The majority of ER positive her

NOTE Confidence: 0.895192625769231

00:49:10.496 --> 00:49:12.444 two negative patients who really

NOTE Confidence: 0.895192625769231

00:49:12.444 --> 00:49:14.748 show show much more modest risk,

NOTE Confidence: 0.866668124666667

00:49:14.750 --> 00:49:16.640 so. Taking this information and comparing

NOTE Confidence: 0.866668124666667

00:49:16.640 --> 00:49:19.359 it to a sort of a typical risk group,

NOTE Confidence: 0.866668124666667

00:49:19.360 --> 00:49:21.110 we built the most powerful

NOTE Confidence: 0.866668124666667

00:49:21.110 --> 00:49:22.510 clinical models we could,

NOTE Confidence: 0.866668124666667

00:49:22.510 --> 00:49:24.610 incorporating all of the known covariates

NOTE Confidence: 0.866668124666667

00:49:24.666 --> 00:49:26.640 and what I'm comparing here is the

NOTE Confidence: 0.866668124666667

00:49:26.640 --> 00:49:28.169 clinical model plus immunohistochemistry

NOTE Confidence: 0.866668124666667

00:49:28.169 --> 00:49:30.677 versus integrative subtype information,

NOTE Confidence: 0.866668124666667

00:49:30.680 --> 00:49:32.525 and what I hope you can appreciate is that

NOTE Confidence: 0.866668124666667

00:49:32.525 --> 00:49:34.315 if we just look at immunohistochemistry

NOTE Confidence: 0.866668124666667

00:49:34.315 --> 00:49:35.845 data to separate these groups,

NOTE Confidence: 0.866668124666667

00:49:35.850 --> 00:49:37.446 we see that the risk is really

NOTE Confidence: 0.866668124666667

00:49:37.446 --> 00:49:38.747 homogenized the green line triangles

NOTE Confidence: 0.866668124666667

00:49:38.747 --> 00:49:40.457 are very similar across these groups,

NOTE Confidence: 0.866668124666667

00:49:40.460 --> 00:49:41.564 whereas when we incorporate

NOTE Confidence: 0.866668124666667

00:49:41.564 --> 00:49:42.116 intricate subtype,

NOTE Confidence: 0.866668124666667

00:49:42.120 --> 00:49:43.896 we see pretty dramatic separation and

NOTE Confidence: 0.866668124666667

00:49:43.896 --> 00:49:46.117 in this varies over time and it varies.

NOTE Confidence: 0.866668124666667

00:49:46.120 --> 00:49:47.113 In a subgroup,

NOTE Confidence: 0.866668124666667

00:49:47.113 --> 00:49:49.099 so we believe that this information

NOTE Confidence: 0.866668124666667

00:49:49.099 --> 00:49:51.260 informs the prediction of relapse risk.

NOTE Confidence: 0.866668124666667

00:49:51.260 --> 00:49:52.580 But critically, you know,

NOTE Confidence: 0.866668124666667

00:49:52.580 --> 00:49:54.560 really these groups have distinct drivers,

NOTE Confidence: 0.866668124666667

00:49:54.560 --> 00:49:56.392 and so I've already talked to you about

NOTE Confidence: 0.866668124666667

00:49:56.392 --> 00:49:58.098 what the integrative subtypes are.

NOTE Confidence: 0.866668124666667

00:49:58.100 --> 00:49:59.822 This is just showing you the

NOTE Confidence: 0.866668124666667

00:49:59.822 --> 00:50:00.970 landscape or amplification frequency

NOTE Confidence: 0.866668124666667

00:50:01.021 --> 00:50:02.257 for these different drivers.

NOTE Confidence: 0.866668124666667

00:50:02.260 --> 00:50:02.922 And really,

NOTE Confidence: 0.866668124666667

00:50:02.922 --> 00:50:04.577 there's many genes in these

NOTE Confidence: 0.866668124666667

00:50:04.577 --> 00:50:06.100 large copy number regions,

NOTE Confidence: 0.866668124666667

00:50:06.100 --> 00:50:07.120 so pinpointing the precise

NOTE Confidence: 0.866668124666667

00:50:07.120 --> 00:50:08.395 driver is a challenging task,

NOTE Confidence: 0.866668124666667

00:50:08.400 --> 00:50:10.320 but there's a number of candidates

NOTE Confidence: 0.866668124666667

00:50:10.320 --> 00:50:12.935 that emerge for each one and just to

NOTE Confidence: 0.866668124666667

00:50:12.935 --> 00:50:14.760 say that while individually these

NOTE Confidence: 0.866668124666667

00:50:14.760 --> 00:50:16.650 groups account for eight or five.

NOTE Confidence: 0.866668124666667

00:50:16.650 --> 00:50:19.384 Or you know, another 8% of the population.

NOTE Confidence: 0.866668124666667

00:50:19.384 --> 00:50:21.854 Together they account for 25% of all,

NOTE Confidence: 0.866668124666667

00:50:21.854 --> 00:50:23.962 ER positive, her two negative cancers,

NOTE Confidence: 0.866668124666667

00:50:23.962 --> 00:50:26.810 and the vast majority of distant relapses.

NOTE Confidence: 0.866668124666667

00:50:26.810 --> 00:50:28.412 And so we've been really intrigued

NOTE Confidence: 0.866668124666667

00:50:28.412 --> 00:50:30.079 to contemplate the fact that this

NOTE Confidence: 0.866668124666667

00:50:30.079 --> 00:50:31.459 may nominate new therapeutic targets

NOTE Confidence: 0.866668124666667

00:50:31.459 --> 00:50:33.119 in these high risk populations,

NOTE Confidence: 0.866668124666667

00:50:33.120 --> 00:50:34.698 thinking about honing in on their

NOTE Confidence: 0.866668124666667

00:50:34.698 --> 00:50:38.008 downstream targets, either the FGFR.

NOTE Confidence: 0.866668124666667

00:50:38.010 --> 00:50:40.446 Receptor itself, or indeed the ligands.

NOTE Confidence: 0.866668124666667

00:50:40.450 --> 00:50:42.075 And of course many downstream

NOTE Confidence: 0.866668124666667

00:50:42.075 --> 00:50:44.260 targets in the AKT mtor pathway.

NOTE Confidence: 0.866668124666667

00:50:44.260 --> 00:50:46.584 And so this actually motivated us to

NOTE Confidence: 0.866668124666667

00:50:46.584 --> 00:50:48.923 develop a window of opportunity trial

NOTE Confidence: 0.866668124666667

00:50:48.923 --> 00:50:51.053 to evaluate new therapeutic strategies

NOTE Confidence: 0.866668124666667

00:50:51.053 --> 00:50:53.348 in these high risk populations,

NOTE Confidence: 0.866668124666667

00:50:53.350 --> 00:50:55.723 and this is funded by the Department

NOTE Confidence: 0.866668124666667

00:50:55.723 --> 00:50:58.230 of Defense and and really this is

NOTE Confidence: 0.866668124666667

00:50:58.230 --> 00:50:59.904 a multicenter trial terpsichore,

NOTE Confidence: 0.866668124666667

00:50:59.904 --> 00:51:02.796 which we will biomarker stratify patients

NOTE Confidence: 0.866668124666667

00:51:02.796 --> 00:51:05.609 according to their integrative subtypes.

NOTE Confidence: 0.866668124666667

00:51:05.610 --> 00:51:08.256 Assign them into these individual groups.

NOTE Confidence: 0.866668124666667

00:51:08.260 --> 00:51:10.500 And conduct a window study where patients

NOTE Confidence: 0.866668124666667

00:51:10.500 --> 00:51:12.598 receive two weeks of targeted therapy.

NOTE Confidence: 0.866668124666667

00:51:12.600 --> 00:51:15.996 The readout of interest is a

NOTE Confidence: 0.866668124666667

00:51:15.996 --> 00:51:18.854 reduction in CHI 67 after therapy,

NOTE Confidence: 0.866668124666667

00:51:18.854 --> 00:51:20.636 and of course we're comparing the

NOTE Confidence: 0.866668124666667

00:51:20.636 --> 00:51:22.462 targeted agent alone or in combination.

NOTE Confidence: 0.866668124666667

00:51:22.462 --> 00:51:22.776 Sorry,

NOTE Confidence: 0.866668124666667

00:51:22.776 --> 00:51:24.660 the targeted agent in combination with

NOTE Confidence: 0.866668124666667

00:51:24.715 --> 00:51:26.779 ending therapy or endocrine therapy alone,

NOTE Confidence: 0.866668124666667

00:51:26.780 --> 00:51:27.876 and they are randomized,

NOTE Confidence: 0.866668124666667

00:51:27.876 --> 00:51:29.520 and so we're really excited about.

NOTE Confidence: 0.866668124666667

00:51:29.520 --> 00:51:30.960 This is a very ambitious trial,

NOTE Confidence: 0.866668124666667

00:51:30.960 --> 00:51:31.512 of course,

NOTE Confidence: 0.866668124666667

00:51:31.512 --> 00:51:33.720 to biomarker stratify in a very short window,

NOTE Confidence: 0.866668124666667

00:51:33.720 --> 00:51:35.232 and to do this in the early stage setting,

NOTE Confidence: 0.866668124666667

00:51:35.240 --> 00:51:36.960 but we believe that additionally,

NOTE Confidence: 0.866668124666667

00:51:36.960 --> 00:51:38.944 by collecting on treatment.

NOTE Confidence: 0.866668124666667

00:51:38.944 --> 00:51:40.904 And core biopsy surgical samples

NOTE Confidence: 0.866668124666667

00:51:40.904 --> 00:51:43.100 will actually be able to conduct

NOTE Confidence: 0.866668124666667

00:51:43.160 --> 00:51:45.212 similar studies to what I described

NOTE Confidence: 0.866668124666667

00:51:45.212 --> 00:51:47.180 before looking at the change in

NOTE Confidence: 0.866668124666667

00:51:47.180 --> 00:51:49.664 in these in these tissue samples

NOTE Confidence: 0.866668124666667

00:51:49.664 --> 00:51:52.419 in response to short term therapy.

NOTE Confidence: 0.866668124666667

00:51:52.420 --> 00:51:53.600 And so to enable this,

NOTE Confidence: 0.866668124666667

00:51:53.600 --> 00:51:55.791 we've really also set up a whole

NOTE Confidence: 0.866668124666667

00:51:55.791 --> 00:51:58.339 pipeline to do prospective biobanking.

NOTE Confidence: 0.866668124666667

00:51:58.340 --> 00:51:59.988 Both plasma tissue collection,

NOTE Confidence: 0.866668124666667

00:51:59.988 --> 00:52:02.460 but also the generation of organoids.

NOTE Confidence: 0.866668124666667

00:52:02.460 --> 00:52:04.086 And I'll say that that's been

NOTE Confidence: 0.866668124666667

00:52:04.086 --> 00:52:05.170 really ongoing work in

NOTE Confidence: 0.920233951923077

00:52:05.226 --> 00:52:06.921 my group to establish organized

NOTE Confidence: 0.920233951923077

00:52:06.921 --> 00:52:08.616 models that are representative of

NOTE Confidence: 0.920233951923077

00:52:08.669 --> 00:52:10.595 these high risk of relapse subgroups,

NOTE Confidence: 0.920233951923077

00:52:10.600 --> 00:52:13.276 because in fact they are vastly

NOTE Confidence: 0.920233951923077

00:52:13.276 --> 00:52:15.540 underrepresented by existing cell lines,

NOTE Confidence: 0.920233951923077

00:52:15.540 --> 00:52:18.020 and this is afforded us a real opportunity

NOTE Confidence: 0.920233951923077

00:52:18.020 --> 00:52:20.101 to have very high quality viable

NOTE Confidence: 0.920233951923077

00:52:20.101 --> 00:52:22.500 material for a number of assays and.

NOTE Confidence: 0.920233951923077

00:52:22.500 --> 00:52:24.201 And I hope to share with you

NOTE Confidence: 0.920233951923077

00:52:24.201 --> 00:52:25.939 some of that at another time,

NOTE Confidence: 0.920233951923077

00:52:25.940 --> 00:52:27.900 but also just to say that this is

NOTE Confidence: 0.920233951923077

00:52:27.900 --> 00:52:29.818 also really fueled a new center that

NOTE Confidence: 0.920233951923077

00:52:29.818 --> 00:52:31.840 we have for breast cancer metastasis.

NOTE Confidence: 0.920233951923077

00:52:31.840 --> 00:52:33.694 It's very much focused on delineating

NOTE Confidence: 0.920233951923077

00:52:33.694 --> 00:52:35.342 the evolutionary dynamics as well

NOTE Confidence: 0.920233951923077

00:52:35.342 --> 00:52:36.778 as micro environmental determinants

NOTE Confidence: 0.920233951923077

00:52:36.778 --> 00:52:38.214 of metastatic breast cancer,

NOTE Confidence: 0.920233951923077

00:52:38.220 --> 00:52:40.355 and it's really oriented around

NOTE Confidence: 0.920233951923077

00:52:40.355 --> 00:52:42.063 these integrative subgroups which

NOTE Confidence: 0.920233951923077

00:52:42.063 --> 00:52:44.019 we've defined seeking to define

NOTE Confidence: 0.920233951923077

00:52:44.019 --> 00:52:45.854 their definitive drivers as well

NOTE Confidence: 0.920233951923077

00:52:45.854 --> 00:52:48.053 as to leverage real-world data

NOTE Confidence: 0.920233951923077

00:52:48.053 --> 00:52:49.825 to evaluate these associations,

NOTE Confidence: 0.920233951923077

00:52:49.830 --> 00:52:52.126 but also to do a deep dive

NOTE Confidence: 0.920233951923077

00:52:52.126 --> 00:52:54.010 into the cellular topography.

NOTE Confidence: 0.920233951923077

00:52:54.010 --> 00:52:56.458 Of both the primary tumor and

NOTE Confidence: 0.920233951923077

00:52:56.458 --> 00:52:57.682 metastasis through therapy.

NOTE Confidence: 0.920233951923077

00:52:57.690 --> 00:52:58.899 And, of course,

NOTE Confidence: 0.920233951923077

00:52:58.899 --> 00:53:00.914 these are inexorably LinkedIn breast

NOTE Confidence: 0.920233951923077

00:53:00.914 --> 00:53:03.100 cancer and then a final piece of this

NOTE Confidence: 0.920233951923077

00:53:03.100 --> 00:53:04.908 and sort of give you the overwhelming

NOTE Confidence: 0.920233951923077

00:53:04.908 --> 00:53:06.996 schematic is actually now with these

NOTE Confidence: 0.920233951923077

00:53:06.996 --> 00:53:08.909 organoid models that we've established.

NOTE Confidence: 0.920233951923077

00:53:08.910 --> 00:53:10.760 We're actually conducting our very

NOTE Confidence: 0.920233951923077

00:53:10.760 --> 00:53:12.910 first crisper screens in 3D models

NOTE Confidence: 0.920233951923077

00:53:12.910 --> 00:53:14.690 to really pinpoint the definitive

NOTE Confidence: 0.920233951923077

00:53:14.756 --> 00:53:16.308 drivers of these subgroups,

NOTE Confidence: 0.920233951923077

00:53:16.310 --> 00:53:17.462 and and of course,

NOTE Confidence: 0.920233951923077

00:53:17.462 --> 00:53:18.902 we hope that this information

NOTE Confidence: 0.920233951923077

00:53:18.910 --> 00:53:21.300 will ultimately inform the next

NOTE Confidence: 0.920233951923077

00:53:21.300 --> 00:53:23.212 wave of clinical trials.

NOTE Confidence: 0.920233951923077

00:53:23.220 --> 00:53:25.572 It's all closed by thanking the many

NOTE Confidence: 0.920233951923077

00:53:25.572 --> 00:53:28.167 people in my lab who led this work.

NOTE Confidence: 0.920233951923077

00:53:28.170 --> 00:53:28.491 Fabulously.

NOTE Confidence: 0.920233951923077

00:53:28.491 --> 00:53:30.417 Talented scientists that it's really a

NOTE Confidence: 0.920233951923077

00:53:30.417 --> 00:53:32.528 privilege for me to work with every day.

NOTE Confidence: 0.920233951923077

00:53:32.530 --> 00:53:33.934 And you saw some of their

NOTE Confidence: 0.920233951923077

00:53:33.934 --> 00:53:34.870 pictures along the way.

NOTE Confidence: 0.920233951923077

00:53:34.870 --> 00:53:37.166 I just want to thank our collaborators at

NOTE Confidence: 0.920233951923077

00:53:37.170 --> 00:53:39.370 Sarah Hurvitz densely man and and Mike Press.

NOTE Confidence: 0.920233951923077

00:53:39.370 --> 00:53:41.442 And of course the initial work was also

NOTE Confidence: 0.920233951923077

00:53:41.442 --> 00:53:43.669 done in collaboration with Nanostring,

NOTE Confidence: 0.920233951923077

00:53:43.670 --> 00:53:46.505 and I'd be very happy to take any questions.

NOTE Confidence: 0.775183734285714

00:53:51.090 --> 00:53:53.058 Great thank you Christina.

NOTE Confidence: 0.775183734285714

00:53:53.058 --> 00:53:54.534 That was terrific.

NOTE Confidence: 0.775183734285714

00:53:54.540 --> 00:53:55.996 Vic lecture and we would all be

NOTE Confidence: 0.775183734285714

00:53:55.996 --> 00:53:58.140 clapping except that you can hear us.

NOTE Confidence: 0.775183734285714

00:53:58.140 --> 00:54:00.508 You can see is the logos these days,

NOTE Confidence: 0.775183734285714

00:54:00.510 --> 00:54:04.406 but I'm sure there must be questions.

NOTE Confidence: 0.775183734285714

00:54:04.410 --> 00:54:05.965 Anyone can either raise their

NOTE Confidence: 0.775183734285714

00:54:05.965 --> 00:54:07.973 hand or if they have questions

NOTE Confidence: 0.775183734285714

00:54:07.973 --> 00:54:09.630 just unmute and go ahead.

NOTE Confidence: 0.61104

00:54:13.560 --> 00:54:15.960 Hi hi Christina, very nice work.

NOTE Confidence: 0.61104

00:54:15.960 --> 00:54:16.990 This is iron crop.

NOTE Confidence: 0.795845276666667

00:54:19.320 --> 00:54:21.664 In the it's a very nice study when

NOTE Confidence: 0.795845276666667

00:54:21.664 --> 00:54:23.794 you have these the the neoadjuvant

NOTE Confidence: 0.795845276666667

00:54:23.794 --> 00:54:26.714 trial with the window of the her two

NOTE Confidence: 0.795845276666667

00:54:26.714 --> 00:54:28.954 therapy alone and you saw that you

NOTE Confidence: 0.795845276666667

00:54:28.954 --> 00:54:31.122 know this decrease in in her two

NOTE Confidence: 0.795845276666667

00:54:31.122 --> 00:54:33.024 signaling and increase in in immune

NOTE Confidence: 0.795845276666667

00:54:33.024 --> 00:54:35.173 markers in the responders or the people

NOTE Confidence: 0.795845276666667

00:54:35.173 --> 00:54:36.855 who eventually would be responders.

NOTE Confidence: 0.795845276666667

00:54:36.855 --> 00:54:40.020 Did you see any difference in that

NOTE Confidence: 0.795845276666667

00:54:40.020 --> 00:54:41.742 association when you looked at the

NOTE Confidence: 0.795845276666667

00:54:41.742 --> 00:54:43.952 type of her two therapy that they

NOTE Confidence: 0.795845276666667

00:54:43.952 --> 00:54:45.950 had given the potential for the

NOTE Confidence: 0.795845276666667

00:54:45.950 --> 00:54:47.811 putative differences met different

NOTE Confidence: 0.795845276666667

00:54:47.811 --> 00:54:49.275 mechanism action between.

NOTE Confidence: 0.795845276666667

00:54:49.280 --> 00:54:50.880 Antibodies and T keys.

NOTE Confidence: 0.816529504

00:54:51.490 --> 00:54:53.722 Yes we did and it was something near

NOTE Confidence: 0.816529504

00:54:53.722 --> 00:54:55.768 and dear to my heart to explore,

NOTE Confidence: 0.816529504

00:54:55.770 --> 00:54:58.702 but I have to say we were pretty

NOTE Confidence: 0.816529504

00:54:58.702 --> 00:55:00.186 underpowered because, you know,

NOTE Confidence: 0.816529504

00:55:00.186 --> 00:55:02.085 the whole trial whole trial was

NOTE Confidence: 0.816529504

00:55:02.085 --> 00:55:04.010 130 patients and then just for the

NOTE Confidence: 0.816529504

00:55:04.071 --> 00:55:06.143 subsets that we did DSP on that that

NOTE Confidence: 0.816529504

00:55:06.143 --> 00:55:07.929 that there was adequate material.

NOTE Confidence: 0.816529504

00:55:07.930 --> 00:55:10.324 The numbers in each of the arms were low.

NOTE Confidence: 0.816529504

00:55:10.330 --> 00:55:12.580 We kind of course grouped the

NOTE Confidence: 0.816529504

00:55:12.580 --> 00:55:14.770 trustees amebo only and the trustees

NOTE Confidence: 0.816529504

00:55:14.770 --> 00:55:17.232 met platinum are we see some hints

NOTE Confidence: 0.816529504

00:55:17.232 --> 00:55:19.020 of signal that would suggest that.

NOTE Confidence: 0.816529504

00:55:19.020 --> 00:55:21.990 You know, ABC mechanisms are are distinct,

NOTE Confidence: 0.816529504

00:55:21.990 --> 00:55:23.834 but we're really underpowered

NOTE Confidence: 0.816529504

00:55:23.834 --> 00:55:26.139 to fully tease that apart,

NOTE Confidence: 0.816529504

00:55:26.140 --> 00:55:27.862 and I think that it's ultimately just

NOTE Confidence: 0.816529504

00:55:27.862 --> 00:55:29.647 going to require a greater sample size,

NOTE Confidence: 0.816529504

00:55:29.650 --> 00:55:30.710 but it's a wonderful question,

NOTE Confidence: 0.816529504

00:55:30.710 --> 00:55:34.710 one that I ruminated on long and hard,

NOTE Confidence: 0.816529504

00:55:34.710 --> 00:55:35.829 and you know,

NOTE Confidence: 0.816529504

00:55:35.829 --> 00:55:38.067 I think I suspect that it's

NOTE Confidence: 0.816529504

00:55:38.067 --> 00:55:40.627 that that it will be different.

NOTE Confidence: 0.816529504

00:55:40.630 --> 00:55:42.010 We just didn't have the data.

NOTE Confidence: 0.816529504

00:55:42.010 --> 00:55:43.560 Yeah, thanks.

NOTE Confidence: 0.4488485674

00:55:48.540 --> 00:55:51.174 Right, this is my year. Thank you.

NOTE Confidence: 0.4488485674

00:55:51.174 --> 00:55:53.809 That was sharing the exciting

NOTE Confidence: 0.4488485674

00:55:53.810 --> 00:55:56.570 part that was really nice.

NOTE Confidence: 0.4488485674

00:55:56.570 --> 00:55:58.678 Difference in the pattern?

NOTE Confidence: 0.4488485674

00:55:58.678 --> 00:56:01.313 You know signature or markers

NOTE Confidence: 0.4488485674

00:56:01.313 --> 00:56:03.576 between the ACB 2 and three?

NOTE Confidence: 0.4488485674

00:56:03.580 --> 00:56:06.210 If y'all look at those or with

NOTE Confidence: 0.4488485674

00:56:06.210 --> 00:56:08.485 ACB 3 just you know worst thing

NOTE Confidence: 0.4488485674

00:56:08.485 --> 00:56:11.077 you know the same type of markers

NOTE Confidence: 0.4488485674

00:56:11.080 --> 00:56:13.768 persisting but much worse.

NOTE Confidence: 0.4488485674

00:56:13.768 --> 00:56:15.596 Yeah, I mean we did.

NOTE Confidence: 0.4488485674

00:56:15.596 --> 00:56:17.041 We did group them again

NOTE Confidence: 0.4488485674

00:56:17.041 --> 00:56:18.410 because of power issues.

NOTE Confidence: 0.4488485674

00:56:18.410 --> 00:56:19.676 You know just in terms of

NOTE Confidence: 0.4488485674

00:56:19.676 --> 00:56:20.520 stratifying further on that.

NOTE Confidence: 0.4488485674

00:56:20.520 --> 00:56:21.936 I agree it would be interesting

NOTE Confidence: 0.4488485674

00:56:21.936 --> 00:56:22.880 we could go back.

NOTE Confidence: 0.4488485674

00:56:22.880 --> 00:56:24.945 I think we're just we're really limited

NOTE Confidence: 0.4488485674

00:56:24.945 --> 00:56:26.878 by the numbers here and you know.

NOTE Confidence: 0.4488485674

00:56:26.880 --> 00:56:29.319 This was intended to be sort of a pilot

NOTE Confidence: 0.4488485674

00:56:29.319 --> 00:56:31.359 effort to understand the technology,

NOTE Confidence: 0.4488485674

00:56:31.360 --> 00:56:33.280 and we went back once we saw these

NOTE Confidence: 0.4488485674

00:56:33.280 --> 00:56:34.919 results and gathered as many samples

NOTE Confidence: 0.4488485674

00:56:34.919 --> 00:56:37.184 from this cohort as we could to go

NOTE Confidence: 0.4488485674

00:56:37.184 --> 00:56:38.828 back and really bolster the numbers,

NOTE Confidence: 0.4488485674

00:56:38.830 --> 00:56:41.053 but I think we're still just just fall short,

NOTE Confidence: 0.4488485674

00:56:41.060 --> 00:56:42.180 and so you know,

NOTE Confidence: 0.4488485674

00:56:42.180 --> 00:56:43.580 I think would be very

NOTE Confidence: 0.4488485674

00:56:43.580 --> 00:56:44.700 interesting to to do this.

NOTE Confidence: 0.4488485674

00:56:44.700 --> 00:56:46.056 Not not that there's so many

NOTE Confidence: 0.4488485674

00:56:46.056 --> 00:56:46.960 of these additional cohorts

NOTE Confidence: 0.4488485674

00:56:47.001 --> 00:56:47.929 that have on treatment,

NOTE Confidence: 0.4488485674

00:56:47.930 --> 00:56:50.380 but there are others that are larger,

NOTE Confidence: 0.4488485674

00:56:50.380 --> 00:56:51.266 so yeah,

NOTE Confidence: 0.4488485674

00:56:51.266 --> 00:56:51.709 unfortunate.

NOTE Confidence: 0.967590635

00:56:54.240 --> 00:56:59.248 Thank you. Both very nice talk.

NOTE Confidence: 0.967590635

00:56:59.250 --> 00:57:01.340 So for the first part of Orlando strain

NOTE Confidence: 0.458792016

00:57:02.050 --> 00:57:05.181 studies when where you showed pretty

NOTE Confidence: 0.458792016

00:57:05.181 --> 00:57:08.367 good prediction power with on treatment

NOTE Confidence: 0.458792016

00:57:08.370 --> 00:57:10.374 parameter but not pre treatment.

NOTE Confidence: 0.458792016

00:57:10.374 --> 00:57:12.150 But I wonder whether you actually

NOTE Confidence: 0.458792016

00:57:12.208 --> 00:57:14.600 look like the the difference or ratio

NOTE Confidence: 0.458792016

00:57:14.600 --> 00:57:16.266 between some of the parameters and

NOTE Confidence: 0.458792016

00:57:16.266 --> 00:57:17.646 see whether there's a correlation.

NOTE Confidence: 0.458792016

00:57:17.650 --> 00:57:19.240 It might be better prediction power,

NOTE Confidence: 0.859905728571429

00:57:19.760 --> 00:57:22.731 that's right so we did so initially many

NOTE Confidence: 0.859905728571429

00:57:22.731 --> 00:57:24.537 of our models were actually combining

NOTE Confidence: 0.859905728571429

00:57:24.537 --> 00:57:26.609 sort of trying to get at this delta.

NOTE Confidence: 0.859905728571429

00:57:26.610 --> 00:57:29.350 The delta which I I thought was going to be,

NOTE Confidence: 0.859905728571429

00:57:29.350 --> 00:57:32.500 you know where it's at?

NOTE Confidence: 0.859905728571429

00:57:32.500 --> 00:57:34.336 Additional information that you're

NOTE Confidence: 0.859905728571429

00:57:34.336 --> 00:57:36.172 leveraging from having these

NOTE Confidence: 0.859905728571429

00:57:36.172 --> 00:57:38.478 pairs and it really turned out.

NOTE Confidence: 0.859905728571429

00:57:38.480 --> 00:57:40.520 That it seems that it's the

NOTE Confidence: 0.859905728571429

00:57:40.520 --> 00:57:42.581 that the on treatment value in

NOTE Confidence: 0.859905728571429

00:57:42.581 --> 00:57:44.453 and of itself held its own.

NOTE Confidence: 0.859905728571429

00:57:44.460 --> 00:57:45.909 It really held its own and we

NOTE Confidence: 0.859905728571429

00:57:45.909 --> 00:57:47.720 didn't get a huge benefit from that.

NOTE Confidence: 0.859905728571429

00:57:47.720 --> 00:57:49.141 Now there there may be many reasons

NOTE Confidence: 0.859905728571429

00:57:49.141 --> 00:57:51.680 why I mean, I'll say that you know,

NOTE Confidence: 0.859905728571429

00:57:51.680 --> 00:57:53.535 we were struck by the reduction in

NOTE Confidence: 0.859905728571429

00:57:53.535 --> 00:57:55.379 celularity in this cohort on treatment.

NOTE Confidence: 0.859905728571429

00:57:55.380 --> 00:57:56.076 Many of these patients,

NOTE Confidence: 0.859905728571429

00:57:56.076 --> 00:57:57.470 and of course we know that you know,

NOTE Confidence: 0.859905728571429

00:57:57.470 --> 00:57:58.844 there's cellularity estimates

NOTE Confidence: 0.859905728571429

00:57:58.844 --> 00:58:00.676 are not always concordant.

NOTE Confidence: 0.859905728571429

00:58:00.680 --> 00:58:03.200 We estimated this both molecularly,

NOTE Confidence: 0.859905728571429

00:58:03.200 --> 00:58:04.790 but obviously with expert pathology

NOTE Confidence: 0.859905728571429

00:58:04.790 --> 00:58:06.761 review and the sections were not

NOTE Confidence: 0.859905728571429

00:58:06.761 --> 00:58:08.376 identical for the different assays,

NOTE Confidence: 0.859905728571429

00:58:08.380 --> 00:58:09.068 of course.

NOTE Confidence: 0.859905728571429

00:58:09.068 --> 00:58:11.820 So there were a number of cases that

NOTE Confidence: 0.859905728571429

00:58:11.894 --> 00:58:14.396 you know had essentially 0 celularity

NOTE Confidence: 0.859905728571429

00:58:14.396 --> 00:58:17.006 upon path review on treatment more

NOTE Confidence: 0.859905728571429

00:58:17.006 --> 00:58:18.448 so than I would have expected we

NOTE Confidence: 0.859905728571429

00:58:18.448 --> 00:58:20.278 see in association with cellularity.

NOTE Confidence: 0.859905728571429

00:58:20.280 --> 00:58:21.792 But of course then what's interesting

NOTE Confidence: 0.859905728571429

00:58:21.792 --> 00:58:24.334 is you go in with DSP and you you start

NOTE Confidence: 0.859905728571429

00:58:24.334 --> 00:58:26.216 to illuminate this and we can see

NOTE Confidence: 0.859905728571429

00:58:26.216 --> 00:58:28.700 evident tumor markers there, right?

NOTE Confidence: 0.859905728571429

00:58:28.700 --> 00:58:30.545 So I mean just coming back to sort of

NOTE Confidence: 0.859905728571429

00:58:30.545 --> 00:58:32.419 some of the questions about the delta,

NOTE Confidence: 0.859905728571429

00:58:32.420 --> 00:58:34.500 I think.

NOTE Confidence: 0.859905728571429

00:58:34.500 --> 00:58:34.872 Yeah.

NOTE Confidence: 0.859905728571429

00:58:34.872 --> 00:58:37.104 You know some some questions emerge

NOTE Confidence: 0.859905728571429

00:58:37.104 --> 00:58:39.161 about like what's the heterogeneity

NOTE Confidence: 0.859905728571429

00:58:39.161 --> 00:58:41.336 in the pretreatment sample versus

NOTE Confidence: 0.859905728571429

00:58:41.336 --> 00:58:42.641 the on treatment?

NOTE Confidence: 0.859905728571429

00:58:42.650 --> 00:58:43.928 We're limited by the core biopsies.

NOTE Confidence: 0.859905728571429

00:58:43.930 --> 00:58:45.900 I think we see quite a bit of it and

NOTE Confidence: 0.859905728571429

00:58:45.962 --> 00:58:47.806 I I would say that we do detail some

NOTE Confidence: 0.859905728571429

00:58:47.806 --> 00:58:49.510 of this in the supplement and methods.

NOTE Confidence: 0.859905728571429

00:58:49.510 --> 00:58:51.092 There's a lot of comparisons one can

NOTE Confidence: 0.859905728571429

00:58:51.092 --> 00:58:53.248 do if you reduce the number of regions,

NOTE Confidence: 0.859905728571429

00:58:53.250 --> 00:58:54.650 which is one way to kind of come

NOTE Confidence: 0.859905728571429

00:58:54.650 --> 00:58:56.308 back to this question of, you know,

NOTE Confidence: 0.859905728571429

00:58:56.308 --> 00:58:57.862 are we measuring enough in terms

NOTE Confidence: 0.859905728571429

00:58:57.862 --> 00:58:58.750 of the delta?

NOTE Confidence: 0.859905728571429

00:58:58.750 --> 00:59:00.661 Because we had some cases for up

NOTE Confidence: 0.859905728571429

00:59:00.661 --> 00:59:02.596 to four ROI's and it looked to us,

NOTE Confidence: 0.859905728571429

00:59:02.600 --> 00:59:03.317 just, you know,

NOTE Confidence: 0.859905728571429

00:59:03.317 --> 00:59:04.990 sort of from a study design consideration

NOTE Confidence: 0.859905728571429

00:59:05.032 --> 00:59:06.286 that a minimum of two regions.

NOTE Confidence: 0.859905728571429

00:59:06.290 --> 00:59:08.690 Would be really helpful here,

NOTE Confidence: 0.859905728571429

00:59:08.690 --> 00:59:11.300 whether for improved that a ton is a you

NOTE Confidence: 0.859905728571429

00:59:11.300 --> 00:59:15.360 know another matter, not always feasible.

NOTE Confidence: 0.859905728571429

00:59:15.360 --> 00:59:16.050 But I think it's a.

NOTE Confidence: 0.859905728571429

00:59:16.050 --> 00:59:17.290 It's a great question that

NOTE Confidence: 0.859905728571429

00:59:17.290 --> 00:59:18.530 was our intuition as well,

NOTE Confidence: 0.859905728571429

00:59:18.530 --> 00:59:19.965 but for these various reasons

NOTE Confidence: 0.859905728571429

00:59:19.965 --> 00:59:21.792 we didn't really see a dramatic

NOTE Confidence: 0.859905728571429

00:59:21.792 --> 00:59:23.116 benefit of the delta.

NOTE Confidence: 0.889476086666667

00:59:26.570 --> 00:59:27.956 Maybe I'll take a chance to

NOTE Confidence: 0.889476086666667

00:59:27.956 --> 00:59:29.330 ask a question here as well.

NOTE Confidence: 0.889476086666667

00:59:29.330 --> 00:59:30.506 We're kind of running out of time,

NOTE Confidence: 0.889476086666667

00:59:30.510 --> 00:59:32.670 but maybe we have a couple more minutes.

NOTE Confidence: 0.889476086666667

00:59:32.670 --> 00:59:34.065 In particular one of those

NOTE Confidence: 0.889476086666667

00:59:34.065 --> 00:59:35.773 things we struggle with is how

NOTE Confidence: 0.889476086666667

00:59:35.773 --> 00:59:37.309 many fields of you are enough,

NOTE Confidence: 0.889476086666667

00:59:37.310 --> 00:59:39.214 and in your DSP study it's it

NOTE Confidence: 0.889476086666667

00:59:39.214 --> 00:59:40.689 looked like that there was.

NOTE Confidence: 0.889476086666667

00:59:40.690 --> 00:59:42.650 You were struggling with that same thing.

NOTE Confidence: 0.889476086666667

00:59:42.650 --> 00:59:44.967 Did you look at in in DSP?

NOTE Confidence: 0.889476086666667

00:59:44.970 --> 00:59:47.168 One of the blessings and curses of

NOTE Confidence: 0.889476086666667

00:59:47.168 --> 00:59:49.087 that technology is it's way more

NOTE Confidence: 0.889476086666667

00:59:49.087 --> 00:59:50.905 data than you can analyze years,

NOTE Confidence: 0.889476086666667

00:59:50.910 --> 00:59:52.611 and there's lots of other questions I

NOTE Confidence: 0.889476086666667

00:59:52.611 --> 00:59:54.526 have for you that I'll discuss later

NOTE Confidence: 0.889476086666667

00:59:54.526 --> 00:59:56.520 about other ways of analyzing that data.

NOTE Confidence: 0.889476086666667

00:59:56.520 --> 00:59:59.112 Did you look at averaging your

NOTE Confidence: 0.889476086666667

00:59:59.112 --> 01:00:01.466 fields of view versus looking at

NOTE Confidence: 0.889476086666667

01:00:01.466 --> 01:00:03.226 them individually and with that

NOTE Confidence: 0.889476086666667

01:00:03.226 --> 01:00:05.390 with the average or individual

NOTE Confidence: 0.889476086666667

01:00:05.390 --> 01:00:06.785 fields more informative?

NOTE Confidence: 0.889476086666667

01:00:06.790 --> 01:00:09.463 And did you look also at like how many

NOTE Confidence: 0.889476086666667

01:00:09.470 --> 01:00:11.437 you know comparing 2 versus 6 that

NOTE Confidence: 0.889476086666667

01:00:11.437 --> 01:00:13.580 looked like you had different numbers?

NOTE Confidence: 0.889476086666667

01:00:13.580 --> 01:00:14.168 Can you comment?

NOTE Confidence: 0.85785495875

01:00:14.180 --> 01:00:14.914 That's right.

NOTE Confidence: 0.85785495875

01:00:14.914 --> 01:00:17.116 Yeah, it's a hugely important question.

NOTE Confidence: 0.85785495875

01:00:17.120 --> 01:00:19.354 I would say we were very.

NOTE Confidence: 0.85785495875

01:00:19.354 --> 01:00:21.730 We spent a lot of time trying to parse

NOTE Confidence: 0.85785495875

01:00:21.795 --> 01:00:24.252 this with this with the data that we had.

NOTE Confidence: 0.85785495875

01:00:24.260 --> 01:00:27.404 I think that some of the analysis I've

NOTE Confidence: 0.85785495875

01:00:27.404 --> 01:00:30.430 presented we did indeed take the average.

NOTE Confidence: 0.85785495875

01:00:30.430 --> 01:00:32.320 There are ways to also,

NOTE Confidence: 0.85785495875

01:00:32.320 --> 01:00:33.900 you know, wait that information,

NOTE Confidence: 0.85785495875

01:00:33.900 --> 01:00:36.444 but in the sort of logistic regression

NOTE Confidence: 0.85785495875

01:00:36.444 --> 01:00:37.954 models we were actually predicting,

NOTE Confidence: 0.85785495875

01:00:37.960 --> 01:00:41.138 we did take an average across them.

NOTE Confidence: 0.85785495875

01:00:41.140 --> 01:00:42.500 We subsequently, you know,

NOTE Confidence: 0.85785495875

01:00:42.500 --> 01:00:44.200 we also investigated sort of.

NOTE Confidence: 0.85785495875

01:00:44.200 --> 01:00:45.110 What if you had only?

NOTE Confidence: 0.85785495875

01:00:45.110 --> 01:00:47.369 One versus 2 versus 4 and some had up

NOTE Confidence: 0.85785495875

01:00:47.369 --> 01:00:49.826 to six and and as I sort of hinted at

NOTE Confidence: 0.85785495875

01:00:49.826 --> 01:00:52.362 and actually analogous to what we've

NOTE Confidence: 0.85785495875

01:00:52.362 --> 01:00:54.384 seen with genomic heterogeneity at

NOTE Confidence: 0.85785495875

01:00:54.384 --> 01:00:56.256 minimum of two regions gets you a lot

NOTE Confidence: 0.85785495875

01:00:56.256 --> 01:00:58.269 this ability to say anything about

NOTE Confidence: 0.85785495875

01:00:58.269 --> 01:00:59.989 how heterogeneous these markers are,

NOTE Confidence: 0.85785495875

01:00:59.990 --> 01:01:03.080 even between sort of two regions

NOTE Confidence: 0.85785495875

01:01:03.080 --> 01:01:04.625 is hugely important,

NOTE Confidence: 0.85785495875

01:01:04.630 --> 01:01:04.902 informative,

NOTE Confidence: 0.85785495875

01:01:04.902 --> 01:01:07.078 and then there starts to be what appears

NOTE Confidence: 0.85785495875

01:01:07.078 --> 01:01:09.328 to be a trail off in terms of the added

NOTE Confidence: 0.85785495875

01:01:09.328 --> 01:01:11.047 benefit when you get up higher to six,

NOTE Confidence: 0.85785495875

01:01:11.050 --> 01:01:11.458 you know,

NOTE Confidence: 0.85785495875

01:01:11.458 --> 01:01:13.090 I think I wouldn't stake my life on

NOTE Confidence: 0.85785495875

01:01:13.142 --> 01:01:14.794 whether choose the absolute Max we we

NOTE Confidence: 0.85785495875

01:01:14.794 --> 01:01:16.537 try to collect more whenever possible

NOTE Confidence: 0.85785495875

01:01:16.537 --> 01:01:18.505 because we're interested in the discovery.

NOTE Confidence: 0.85785495875

01:01:18.510 --> 01:01:18.924 You know,

NOTE Confidence: 0.85785495875

01:01:18.924 --> 01:01:20.166 and sort of questions around this.

NOTE Confidence: 0.85785495875

01:01:20.170 --> 01:01:22.519 And I, I think also questions arise as to,

NOTE Confidence: 0.85785495875

01:01:22.520 --> 01:01:24.167 you know how variable is this going to be

NOTE Confidence: 0.85785495875

01:01:24.167 --> 01:01:27.330 for different subgroups of disease, right?

NOTE Confidence: 0.85785495875

01:01:27.330 --> 01:01:28.996 So I don't think we've mastered that,

NOTE Confidence: 0.85785495875

01:01:29.000 --> 01:01:31.718 but I felt at least encouraged that with two.

NOTE Confidence: 0.85785495875

01:01:31.720 --> 01:01:34.584 We seem to be gaining information that that

NOTE Confidence: 0.85785495875

01:01:34.584 --> 01:01:36.720 the heterogeneity itself was informative.

NOTE Confidence: 0.85785495875

01:01:36.720 --> 01:01:36.990 Yeah,

NOTE Confidence: 0.85785495875

01:01:37.570 --> 01:01:39.680 great thanks.

NOTE Confidence: 0.920342458

01:01:39.680 --> 01:01:40.660 Are there any other questions?

NOTE Confidence: 0.920342458

01:01:40.660 --> 01:01:42.440 Were already 5 minutes past,

NOTE Confidence: 0.920342458

01:01:42.440 --> 01:01:44.180 but if there's one more question,

NOTE Confidence: 0.920342458

01:01:44.180 --> 01:01:45.566 maybe we could take that if not.

NOTE Confidence: 0.913292115714286

01:01:47.750 --> 01:01:49.787 I don't see anyone raising their hands,

NOTE Confidence: 0.913292115714286

01:01:49.790 --> 01:01:52.748 so I'll assume that we're all

NOTE Confidence: 0.913292115714286

01:01:52.750 --> 01:01:54.520 happy with where we are and

NOTE Confidence: 0.913292115714286

01:01:54.520 --> 01:01:56.838 thank you very much for a very

NOTE Confidence: 0.913292115714286

01:01:56.838 --> 01:01:58.530 interesting lecture and well, thank.

NOTE Confidence: 0.913292115714286

01:01:58.530 --> 01:02:00.080 Thank you all for joining.

NOTE Confidence: 0.9328743

01:02:01.280 --> 01:02:01.750 Thank you.