WEBVTT

NOTE duration:"00:59:41"

NOTE recognizability:0.788

NOTE language:en-us

NOTE Confidence: 0.847751033636364

00:00:00.000 --> 00:00:02.025 I'm doctor Mary. I'm lustberg.

NOTE Confidence: 0.847751033636364

00:00:02.025 --> 00:00:04.790 Thank you for joining in person and

NOTE Confidence: 0.847751033636364

00:00:04.790 --> 00:00:06.740 for those of you joining online.

NOTE Confidence: 0.928668915

00:00:09.780 --> 00:00:14.494 I'm pleased to introduce Doctor Louis

NOTE Confidence: 0.928668915

00:00:14.494 --> 00:00:19.320 Pushti as today's ground round speaker.

NOTE Confidence: 0.928668915

00:00:19.320 --> 00:00:22.470 Doctor Pushki is professor of medicine.

NOTE Confidence: 0.928668915

00:00:22.470 --> 00:00:24.770 And Co director of the genomics,

NOTE Confidence: 0.928668915

00:00:24.770 --> 00:00:26.411 genetics and Epigenetics

NOTE Confidence: 0.928668915

00:00:26.411 --> 00:00:29.146 Research program here at Yale.

NOTE Confidence: 0.928668915

00:00:29.150 --> 00:00:31.500 He received his medical degree

NOTE Confidence: 0.928668915

00:00:31.500 --> 00:00:33.580 from Semmelweis University of

NOTE Confidence: 0.928668915

00:00:33.580 --> 00:00:37.057 Medicine in Budapest and his Doctor

NOTE Confidence: 0.928668915

00:00:37.057 --> 00:00:39.302 of Philosophy degree from the

NOTE Confidence: 0.928668915

00:00:39.302 --> 00:00:41.679 University of Oxford in England.

NOTE Confidence: 0.928668915

00:00:41.680 --> 00:00:44.105 His research group has made

NOTE Confidence: 0.928668915

00:00:44.105 --> 00:00:46.045 important contributions to establish

NOTE Confidence: 0.928668915

00:00:46.045 --> 00:00:48.358 that estrogen receptor positive

NOTE Confidence: 0.928668915

00:00:48.358 --> 00:00:51.278 and negative breast cancers have

NOTE Confidence: 0.928668915

00:00:51.278 --> 00:00:53.220 fundamentally different molecular,

NOTE Confidence: 0.928668915

00:00:53.220 --> 00:00:57.860 clinical and epidemiological characteristics.

NOTE Confidence: 0.928668915

00:00:57.860 --> 00:01:01.046 He's been a pioneer in evaluating

NOTE Confidence: 0.928668915

00:01:01.046 --> 00:01:03.170 gene expression profiling as

NOTE Confidence: 0.928668915

00:01:03.262 --> 00:01:05.320 a diagnostic technology.

NOTE Confidence: 0.928668915

00:01:05.320 --> 00:01:08.580 To predict chemotherapy and

NOTE Confidence: 0.928668915

00:01:08.580 --> 00:01:11.025 endocrine therapy sensitivity.

NOTE Confidence: 0.928668915

00:01:11.030 --> 00:01:13.946 And as shown that different biological

NOTE Confidence: 0.928668915

00:01:13.950 --> 00:01:16.438 processes are involved in determining

NOTE Confidence: 0.928668915

00:01:16.438 --> 00:01:18.950 the prognosis and treatment response

NOTE Confidence: 0.928668915

00:01:18.950 --> 00:01:23.090 in different breast cancer subtype.

NOTE Confidence: 0.928668915

00:01:23.090 --> 00:01:25.976 His group has also developed new

NOTE Confidence: 0.928668915

00:01:25.976 --> 00:01:27.900 bioinformatics tools to integrate

NOTE Confidence: 0.928668915

00:01:27.982 --> 00:01:29.938 information from across different

NOTE Confidence: 0.928668915

00:01:29.938 --> 00:01:32.872 data platforms in order to define

NOTE Confidence: 0.928668915

00:01:32.947 --> 00:01:35.207 the molecular pathways that are

NOTE Confidence: 0.928668915

00:01:35.210 --> 00:01:37.490 disturbed in individual cancers

NOTE Confidence: 0.928668915

00:01:37.490 --> 00:01:39.990 and could provide the basis.

NOTE Confidence: 0.928668915

00:01:39.990 --> 00:01:42.770 For individualized treatment strategies.

NOTE Confidence: 0.796025125714286

00:01:45.370 --> 00:01:47.542 Doctor Pushki is a trusted colleague

NOTE Confidence: 0.796025125714286

00:01:47.542 --> 00:01:50.446 here at Yale and is a principal

NOTE Confidence: 0.796025125714286

00:01:50.446 --> 00:01:51.990 investigator of several clinical

NOTE Confidence: 0.796025125714286

00:01:51.990 --> 00:01:54.770 trials investigating new drugs,

NOTE Confidence: 0.796025125714286

00:01:54.770 --> 00:01:58.245 including immunotherapies for breast cancer.

NOTE Confidence: 0.796025125714286

00:01:58.250 --> 00:02:01.500 He's published over 250 scientific

NOTE Confidence: 0.796025125714286

00:02:01.500 --> 00:02:05.283 manuscripts in high impact medical journals

NOTE Confidence: 0.796025125714286

00:02:05.283 --> 00:02:09.090 and is among the top 1% most highly

NOTE Confidence: 0.796025125714286

00:02:09.090 --> 00:02:12.140 cited clinical investigators in medicine

NOTE Confidence: 0.9487658

00:02:12.150 --> 00:02:13.350 over the past 10 years.

NOTE Confidence: 0.859605108333333

00:02:14.960 --> 00:02:17.520 Today he will speak on breast cancer,

NOTE Confidence: 0.859605108333333

00:02:17.520 --> 00:02:21.200 moving ever closer to cure for all.

NOTE Confidence: 0.859605108333333

00:02:21.200 --> 00:02:22.856 Thank you so much Doctor Pushkar.

NOTE Confidence: 0.88288054

00:02:28.940 --> 00:02:31.136 You can go ahead and start using this.

NOTE Confidence: 0.88288054

00:02:31.136 --> 00:02:31.994 Thank you, Mary.

NOTE Confidence: 0.88288054

00:02:31.994 --> 00:02:34.020 I'm so if you're OK with you,

NOTE Confidence: 0.88288054

00:02:34.020 --> 00:02:35.616 I will take this mask off because

NOTE Confidence: 0.88288054

00:02:35.616 --> 00:02:37.392 having a mask, my accent and my

NOTE Confidence: 0.88288054

00:02:37.392 --> 00:02:38.757 voice would be really serious.

NOTE Confidence: 0.88288054

00:02:38.760 --> 00:02:41.640 Triple hit against me from the get go.

NOTE Confidence: 0.88288054

00:02:41.640 --> 00:02:43.936 So I hope it's OK with you.

NOTE Confidence: 0.88288054

00:02:43.940 --> 00:02:45.554 It's delighted to see that some

NOTE Confidence: 0.88288054

00:02:45.554 --> 00:02:47.334 people are in the auditorium because

NOTE Confidence: 0.88288054

00:02:47.334 --> 00:02:49.595 I actually forgot how to get here.

NOTE Confidence: 0.88288054

00:02:49.600 --> 00:02:52.444 So I really sympathize with those of

NOTE Confidence: 0.88288054

00:02:52.444 --> 00:02:54.488 you who are actually online with this.

NOTE Confidence: 0.88288054

00:02:54.490 --> 00:02:58.480 So I think I need to start

NOTE Confidence: 0.88288054

00:02:58.480 --> 00:03:01.210 with my disclosure slides.

NOTE Confidence: 0.88288054

00:03:01.210 --> 00:03:03.289 And then before I start my slides,

NOTE Confidence: 0.88288054

00:03:03.290 --> 00:03:05.180 I would actually like to make a

NOTE Confidence: 0.88288054

00:03:05.180 --> 00:03:07.207 confession to you and admit a weakness.

NOTE Confidence: 0.88288054

00:03:07.210 --> 00:03:07.999 It's not chocolate,

NOTE Confidence: 0.88288054

00:03:07.999 --> 00:03:10.367 but I do feel like a child in a

NOTE Confidence: 0.88288054

00:03:10.367 --> 00:03:12.005 in a candy store surrounded by a

NOTE Confidence: 0.88288054

00:03:12.005 --> 00:03:14.517 lot of really delicious and very

NOTE Confidence: 0.88288054

00:03:14.517 --> 00:03:15.846 interesting scientific questions.

NOTE Confidence: 0.88288054

00:03:15.850 --> 00:03:18.271 So my weakness is that I have a really

NOTE Confidence: 0.88288054

00:03:18.271 --> 00:03:20.545 eclectic and very broad range of interests.

NOTE Confidence: 0.88288054

00:03:20.550 --> 00:03:21.414 And don't be scared,

NOTE Confidence: 0.88288054

00:03:21.414 --> 00:03:23.013 I'm not going to talk about all

NOTE Confidence: 0.88288054

00:03:23.013 --> 00:03:23.787 of these questions,

NOTE Confidence: 0.88288054

00:03:23.790 --> 00:03:25.870 but these are the type of questions that.

NOTE Confidence: 0.88288054

00:03:25.870 --> 00:03:28.005 My group has been studying in the

NOTE Confidence: 0.88288054

00:03:28.005 --> 00:03:30.390 past few years and I showed this here

NOTE Confidence: 0.88288054

00:03:30.390 --> 00:03:32.427 for you to forgive me and understand

NOTE Confidence: 0.88288054

00:03:32.427 --> 00:03:36.710 why I don't show up to most of the.

NOTE Confidence: 0.88288054

00:03:36.710 --> 00:03:37.638 Administrative meetings,

NOTE Confidence: 0.88288054

00:03:37.638 --> 00:03:39.958 so these studying things like

NOTE Confidence: 0.88288054

00:03:39.958 --> 00:03:40.886 cost effectiveness,

NOTE Confidence: 0.88288054

00:03:40.890 --> 00:03:42.460 what's the best cost effective

NOTE Confidence: 0.88288054

00:03:42.460 --> 00:03:44.030 strategy in the new adjuvant

NOTE Confidence: 0.88288054

00:03:44.090 --> 00:03:45.690 setting for for breast cancer,

NOTE Confidence: 0.88288054

00:03:45.690 --> 00:03:47.382 why some preoperative chemotherapy

NOTE Confidence: 0.88288054

00:03:47.382 --> 00:03:49.497 regimens produce high response rates

NOTE Confidence: 0.88288054

00:03:49.497 --> 00:03:51.723 but very little improvement in survival

NOTE Confidence: 0.88288054

00:03:51.723 --> 00:03:53.984 and other regiments to the opposite

NOTE Confidence: 0.88288054

00:03:53.984 --> 00:03:55.788 small improvements in response,

NOTE Confidence: 0.88288054

00:03:55.790 --> 00:03:57.330 large improvements in survival.

NOTE Confidence: 0.88288054

00:03:57.330 --> 00:04:00.077 Why there is some women develop breast

NOTE Confidence: 0.88288054

00:04:00.077 --> 00:04:02.646 cancer 20-30 years before the median age?

NOTE Confidence: 0.88288054

00:04:02.650 --> 00:04:04.810 Could we develop some sort of a tool to

NOTE Confidence: 0.88288054

00:04:04.810 --> 00:04:06.958 sum up all the genomic abnormalities?

NOTE Confidence: 0.88288054

00:04:06.960 --> 00:04:09.366 From germline and somatic regions that

NOTE Confidence: 0.88288054

00:04:09.366 --> 00:04:11.432 would actually describe the capture

NOTE Confidence: 0.88288054

00:04:11.432 --> 00:04:13.826 the totality of abnormalities in atom.

NOTE Confidence: 0.88288054

00:04:13.830 --> 00:04:15.888 How comes that summer stragen receptor

NOTE Confidence: 0.88288054

00:04:15.888 --> 00:04:18.289 positive cancers recur as they are negative?

NOTE Confidence: 0.88288054

00:04:18.290 --> 00:04:20.168 You know some ER positive cancers

NOTE Confidence: 0.88288054

00:04:20.168 --> 00:04:22.050 are not fully ER positive,

NOTE Confidence: 0.88288054

00:04:22.050 --> 00:04:22.656 3040% positive.

NOTE Confidence: 0.88288054

00:04:22.656 --> 00:04:25.080 So what are the rest of those cells

NOTE Confidence: 0.88288054

00:04:25.142 --> 00:04:26.450 which are ER negative?

NOTE Confidence: 0.88288054

00:04:26.450 --> 00:04:28.385 What's their relationship to the

NOTE Confidence: 0.88288054

00:04:28.385 --> 00:04:29.546 ER positive cells?

NOTE Confidence: 0.88288054

00:04:29.550 --> 00:04:31.968 What novel therapeutic strategies one could

NOTE Confidence: 0.88288054

00:04:31.968 --> 00:04:35.308 dig out from high dimensional genomic data.

NOTE Confidence: 0.88288054

00:04:35.310 --> 00:04:37.920 So what is the molecular phylogenetic

NOTE Confidence: 0.88288054

00:04:37.920 --> 00:04:39.225 relationship between different

NOTE Confidence: 0.88288054

00:04:39.225 --> 00:04:41.367 metastatic lesions and the primary tumor?

NOTE Confidence: 0.88288054

00:04:41.370 --> 00:04:43.205 Is these different for synchronous

NOTE Confidence: 0.88288054

00:04:43.205 --> 00:04:44.306 mats against asynchronous?

NOTE Confidence: 0.88288054

00:04:44.310 --> 00:04:46.515 That's you know why some Kansas are

NOTE Confidence: 0.88288054

00:04:46.515 --> 00:04:48.478 immune reaction immune poor was the

NOTE Confidence: 0.88288054

00:04:48.478 --> 00:04:50.398 difference between the immune rich ER

NOTE Confidence: 0.88288054

00:04:50.398 --> 00:04:52.407 positive and PR negative terms is there

NOTE Confidence: 0.88288054

00:04:52.407 --> 00:04:54.064 a difference in the microenvironment

NOTE Confidence: 0.88288054

00:04:54.064 --> 00:04:57.448 that's race influence this so really

NOTE Confidence: 0.88288054

00:04:57.448 --> 00:05:00.679 study all of these things and.

NOTE Confidence: 0.88288054

00:05:00.680 --> 00:05:02.400 You can look at the publications on them.

NOTE Confidence: 0.88288054

00:05:02.400 --> 00:05:04.176 So I'm only going to focus on a

NOTE Confidence: 0.88288054

00:05:04.176 --> 00:05:06.170 few which I think have a longer

NOTE Confidence: 0.88288054

00:05:06.170 --> 00:05:08.012 trajectory and contributed to the to

NOTE Confidence: 0.88288054

00:05:08.012 --> 00:05:09.477 this remarkable events that happened

NOTE Confidence: 0.88288054

00:05:09.477 --> 00:05:11.991 in the past 20 years that breast

NOTE Confidence: 0.88288054

00:05:11.991 --> 00:05:14.226 cancer survival and mortality decline,

NOTE Confidence: 0.88288054

00:05:14.230 --> 00:05:16.840 mortality decline by about 50%.

NOTE Confidence: 0.88288054

00:05:16.840 --> 00:05:18.796 I think this is primarily driven

NOTE Confidence: 0.88288054

00:05:18.796 --> 00:05:20.461 by new treatment strategies based

NOTE Confidence: 0.88288054

00:05:20.461 --> 00:05:21.981 on better understanding of the

NOTE Confidence: 0.88288054

00:05:21.981 --> 00:05:23.197 disease and the new

NOTE Confidence: 0.88220373

00:05:23.257 --> 00:05:25.159 classes of drugs that we developed.

NOTE Confidence: 0.88220373

00:05:25.160 --> 00:05:27.338 And I think the journey is

NOTE Confidence: 0.88220373

00:05:27.338 --> 00:05:29.360 just just about to begin.

NOTE Confidence: 0.88220373

00:05:29.360 --> 00:05:32.310 So how new treatment strategies

NOTE Confidence: 0.88220373

00:05:32.310 --> 00:05:34.080 could influence outcome?

NOTE Confidence: 0.88220373

00:05:34.080 --> 00:05:36.480 So in the early 2000s,

NOTE Confidence: 0.88220373

00:05:36.480 --> 00:05:38.461 I was in the right place at

NOTE Confidence: 0.88220373

00:05:38.461 --> 00:05:40.390 the right time at MD Anderson,

NOTE Confidence: 0.88220373

00:05:40.390 --> 00:05:42.045 we were interested to explore

NOTE Confidence: 0.88220373

00:05:42.045 --> 00:05:43.038 period preoperative chemotherapy

NOTE Confidence: 0.88220373

00:05:43.038 --> 00:05:44.821 for women who actually had operable

NOTE Confidence: 0.88220373

00:05:44.821 --> 00:05:46.423 disease and we assumed that they

NOTE Confidence: 0.88220373

00:05:46.472 --> 00:05:48.208 would end up with a better cosmetic

NOTE Confidence: 0.88220373

00:05:48.208 --> 00:05:49.288 outcome as smaller disease.

NOTE Confidence: 0.88220373

00:05:49.288 --> 00:05:50.600 And at that time,

NOTE Confidence: 0.88220373

00:05:50.600 --> 00:05:52.346 it was a pretty controversial idea

NOTE Confidence: 0.88220373

00:05:52.346 --> 00:05:54.405 and there was really no good way

NOTE Confidence: 0.88220373

00:05:54.405 --> 00:05:55.795 to either define the response.

NOTE Confidence: 0.88220373

00:05:55.800 --> 00:05:57.360 How do you measure the efficacy

NOTE Confidence: 0.88220373

00:05:57.360 --> 00:05:58.400 of these preoperative regiments?

NOTE Confidence: 0.88220373

00:05:58.400 --> 00:06:00.176 Do you measure it by response?

NOTE Confidence: 0.88220373

00:06:00.180 --> 00:06:01.980 On imaging or we measured by

NOTE Confidence: 0.88220373

00:06:01.980 --> 00:06:03.720 the extent of residual disease.

NOTE Confidence: 0.88220373

00:06:03.720 --> 00:06:05.634 So we proposed the the definition

NOTE Confidence: 0.88220373

00:06:05.634 --> 00:06:07.292 which eventually become the standard

NOTE Confidence: 0.88220373

00:06:07.292 --> 00:06:09.236 of care definition that you have

NOTE Confidence: 0.88220373

00:06:09.236 --> 00:06:11.069 no residual invasive cancer in the

NOTE Confidence: 0.88220373

00:06:11.069 --> 00:06:12.938 breast or lymph nodes and that's kind

NOTE Confidence: 0.88220373

00:06:12.940 --> 00:06:14.916 of the best outcome that you could get.

NOTE Confidence: 0.88220373

00:06:14.920 --> 00:06:17.212 So with this definition it pretty

NOTE Confidence: 0.88220373

00:06:17.212 --> 00:06:18.740 quickly become available become

NOTE Confidence: 0.88220373

00:06:18.803 --> 00:06:20.919 obvious that individuals accomplish

NOTE Confidence: 0.88220373

00:06:20.919 --> 00:06:23.035 this complete pathological response.

NOTE Confidence: 0.88220373

00:06:23.040 --> 00:06:24.516 It really well regardless of what

NOTE Confidence: 0.88220373

00:06:24.516 --> 00:06:25.949 type of breast cancer they had,

NOTE Confidence: 0.88220373

00:06:25.950 --> 00:06:27.665 they are positive or negative

NOTE Confidence: 0.88220373

00:06:27.665 --> 00:06:28.694 or too positive.

NOTE Confidence: 0.88220373

00:06:28.700 --> 00:06:30.924 Those who had residual disease didn't do so.

NOTE Confidence: 0.88220373

00:06:30.930 --> 00:06:32.841 And this immediately defines you what you

NOTE Confidence: 0.88220373

00:06:32.841 --> 00:06:34.887 actually want to accomplish in the clinic,

NOTE Confidence: 0.88220373

00:06:34.890 --> 00:06:35.180 right?

NOTE Confidence: 0.88220373

00:06:35.180 --> 00:06:36.920 You want to put more patients

NOTE Confidence: 0.88220373

00:06:36.920 --> 00:06:38.322 into these pathologic CR category

NOTE Confidence: 0.88220373

00:06:38.322 --> 00:06:39.750 and you want to hurt harm.

NOTE Confidence: 0.88220373

00:06:39.750 --> 00:06:41.689 Do you wanna help those who are

NOTE Confidence: 0.88220373

00:06:41.689 --> 00:06:43.410 in the residual disease group?

NOTE Confidence: 0.88220373

00:06:43.410 --> 00:06:45.300 So we did that in the past 20 years.

NOTE Confidence: 0.88220373

00:06:45.300 --> 00:06:49.930 So you see the evolution of the chemotherapy.

NOTE Confidence: 0.88220373

00:06:49.930 --> 00:06:50.222 Regiments,

NOTE Confidence: 0.88220373

00:06:50.222 --> 00:06:51.974 in 2008 when we published this

NOTE Confidence: 0.88220373

00:06:51.974 --> 00:06:53.769 paper on the survival curves,

NOTE Confidence: 0.88220373

00:06:53.770 --> 00:06:55.302 the best chemotherapy was

NOTE Confidence: 0.88220373

00:06:55.302 --> 00:06:56.068 Taxol anthracyclines.

NOTE Confidence: 0.88220373

00:06:56.070 --> 00:06:58.070 It produced about a 3035%

NOTE Confidence: 0.88220373

00:06:58.070 --> 00:06:59.466 response complete response rate,

NOTE Confidence: 0.88220373

00:06:59.466 --> 00:07:00.862 in particular negative disease

NOTE Confidence: 0.88220373

00:07:00.862 --> 00:07:02.648 and now we have doubled that.

NOTE Confidence: 0.88220373

00:07:02.650 --> 00:07:04.450 So now we actually accomplish

NOTE Confidence: 0.88220373

00:07:04.450 --> 00:07:06.794 about a 63% complete response rate

NOTE Confidence: 0.88220373

00:07:06.794 --> 00:07:08.824 by adding an immunotherapy drug.

NOTE Confidence: 0.88220373

00:07:08.830 --> 00:07:11.224 And you also learn that adding other

NOTE Confidence: 0.88220373

00:07:11.224 --> 00:07:12.727 chemotherapy agents like carboplatin

NOTE Confidence: 0.88220373

00:07:12.727 --> 00:07:14.827 improves the pathologic CR rates.

NOTE Confidence: 0.88220373

00:07:14.830 --> 00:07:16.370 We have regiments that don't

NOTE Confidence: 0.88220373

00:07:16.370 --> 00:07:17.602 include the anthracyclines that

NOTE Confidence: 0.88220373

00:07:17.602 --> 00:07:19.286 some of my colleagues think that.

NOTE Confidence: 0.88220373

00:07:19.290 --> 00:07:21.936 Is the chemical incarnation of the devil.

NOTE Confidence: 0.88220373

00:07:21.940 --> 00:07:24.894 Also there are even single agent therapies,

NOTE Confidence: 0.88220373

00:07:24.900 --> 00:07:27.170 targeted therapies like PARP inhibitors

NOTE Confidence: 0.88220373

00:07:27.170 --> 00:07:28.986 that produce pretty respectable

NOTE Confidence: 0.88220373

00:07:28.986 --> 00:07:30.660 pathology company eradication of

NOTE Confidence: 0.88220373

00:07:30.660 --> 00:07:33.104 the cancer before surgery in in

NOTE Confidence: 0.88220373

00:07:33.104 --> 00:07:34.460 germline Brockhampton patients.

NOTE Confidence: 0.88220373

00:07:34.460 --> 00:07:36.868 But we also made him really important

NOTE Confidence: 0.88220373

00:07:36.868 --> 00:07:38.964 improvements for in the life of

NOTE Confidence: 0.88220373

00:07:38.964 --> 00:07:40.624 those who have residual disease.

NOTE Confidence: 0.88220373

00:07:40.630 --> 00:07:42.634 So those are three randomized clinical

NOTE Confidence: 0.88220373

00:07:42.634 --> 00:07:44.321 trials that established the value

NOTE Confidence: 0.88220373

00:07:44.321 --> 00:07:45.791 of giving capsidae in chemotherapy

NOTE Confidence: 0.88220373

00:07:45.791 --> 00:07:47.778 for those and the residual disease

NOTE Confidence: 0.88220373

00:07:47.778 --> 00:07:49.298 with triple negative cancer.

NOTE Confidence: 0.88220373

00:07:49.300 --> 00:07:51.430 And the Olympia study showed that

NOTE Confidence: 0.88220373

00:07:51.430 --> 00:07:53.026 that whole party improves the

NOTE Confidence: 0.88220373

00:07:53.026 --> 00:07:54.571 response within a similar population

NOTE Confidence: 0.88220373

00:07:54.571 --> 00:07:56.329 if the average germline Broca's.

NOTE Confidence: 0.88220373

00:07:56.330 --> 00:07:58.106 And the Catherine study did the

NOTE Confidence: 0.88220373

00:07:58.106 --> 00:08:00.193 same for the record TDM one or

NOTE Confidence: 0.88220373

00:08:00.193 --> 00:08:02.146 Godzilla for her to post the disease.

NOTE Confidence: 0.88220373

00:08:02.150 --> 00:08:03.860 But I want to spend a few minutes on

NOTE Confidence: 0.88220373

00:08:03.860 --> 00:08:06.158 how do we get there, in particular,

NOTE Confidence: 0.88220373

00:08:06.158 --> 00:08:10.662 how we actually came about to establish

NOTE Confidence: 0.88220373

00:08:10.662 --> 00:08:13.877 the value of immunotherapy in.

NOTE Confidence: 0.798355488695652

00:08:13.880 --> 00:08:16.036 In breast cancer. So the roots of

NOTE Confidence: 0.798355488695652

00:08:16.036 --> 00:08:17.827 this idea that immunotherapy might

NOTE Confidence: 0.798355488695652

00:08:17.827 --> 00:08:20.215 work in breast cancer has been

NOTE Confidence: 0.798355488695652

00:08:20.215 --> 00:08:22.560 long rooted in preclinical studies.

NOTE Confidence: 0.798355488695652

00:08:22.560 --> 00:08:24.912 But also in the early 2000s a number

NOTE Confidence: 0.798355488695652

00:08:24.912 --> 00:08:27.775 of of groups reported that even in

NOTE Confidence: 0.798355488695652

00:08:27.775 --> 00:08:29.980 patients who only receive surgery,

NOTE Confidence: 0.798355488695652

00:08:29.980 --> 00:08:32.532 the amount of immune cells in the tumor

NOTE Confidence: 0.798355488695652

00:08:32.532 --> 00:08:34.200 microenvironment is hugely prognostic.

NOTE Confidence: 0.798355488695652

00:08:34.200 --> 00:08:36.216 So this is what the the first half of

NOTE Confidence: 0.798355488695652

00:08:36.216 --> 00:08:37.983 this slide shows you survival curves

NOTE Confidence: 0.798355488695652

00:08:37.983 --> 00:08:39.897 for patients who did not receive

NOTE Confidence: 0.798355488695652

00:08:39.897 --> 00:08:41.717 any other treatment than surgery,

NOTE Confidence: 0.798355488695652

00:08:41.720 --> 00:08:44.048 they were stratified into three groups.

NOTE Confidence: 0.798355488695652

00:08:44.050 --> 00:08:45.566 Little high immune presence,

NOTE Confidence: 0.798355488695652

00:08:45.566 --> 00:08:47.461 intermediate in presence or low

NOTE Confidence: 0.798355488695652

00:08:47.461 --> 00:08:49.341 immune presence and you see that

NOTE Confidence: 0.798355488695652

00:08:49.341 --> 00:08:51.502 that the the immune cells have a

NOTE Confidence: 0.798355488695652

00:08:51.502 --> 00:08:53.470 massive prognostic value in all three

NOTE Confidence: 0.798355488695652

00:08:53.470 --> 00:08:55.646 categories of of breast cancer subtypes

NOTE Confidence: 0.798355488695652

00:08:55.646 --> 00:08:57.920 including the the ER positive patients.

NOTE Confidence: 0.798355488695652

00:08:57.920 --> 00:08:59.656 And what we used in this particular

NOTE Confidence: 0.798355488695652

00:08:59.656 --> 00:09:01.452 study was gene signature to define

NOTE Confidence: 0.798355488695652

00:09:01.452 --> 00:09:02.445 the immune richness.

NOTE Confidence: 0.798355488695652

00:09:02.450 --> 00:09:04.850 They're in the same time German

NOTE Confidence: 0.798355488695652

00:09:04.850 --> 00:09:06.450 investigators showed that that

NOTE Confidence: 0.798355488695652

00:09:06.518 --> 00:09:08.840 the presence of immune cells also

NOTE Confidence: 0.798355488695652

00:09:08.840 --> 00:09:10.670 predicts the probability of complete

NOTE Confidence: 0.798355488695652

00:09:10.670 --> 00:09:11.390 pathological response.

NOTE Confidence: 0.798355488695652

00:09:11.390 --> 00:09:14.292 But this slide shows you 32 important things.

NOTE Confidence: 0.798355488695652

00:09:14.292 --> 00:09:16.929 One is that in the red circles you

NOTE Confidence: 0.798355488695652

00:09:16.929 --> 00:09:18.814 see the pathologic computer response

NOTE Confidence: 0.798355488695652

00:09:18.814 --> 00:09:22.538 rates by tumor infiltrating into side.

NOTE Confidence: 0.798355488695652

00:09:22.540 --> 00:09:22.893 Presence.

NOTE Confidence: 0.798355488695652

00:09:22.893 --> 00:09:25.011 So they grouped the cases into

NOTE Confidence: 0.798355488695652

00:09:25.011 --> 00:09:26.430 no lymphocytes, some lymphocytes,

NOTE Confidence: 0.798355488695652

00:09:26.430 --> 00:09:27.850 lymphocyte predominant and you

NOTE Confidence: 0.798355488695652

00:09:27.850 --> 00:09:29.810 see that the pathologic CR rates

NOTE Confidence: 0.798355488695652

00:09:29.810 --> 00:09:31.504 these numbers in the in the little

NOTE Confidence: 0.798355488695652

00:09:31.504 --> 00:09:33.251 blood red circles increase as you

NOTE Confidence: 0.798355488695652

00:09:33.251 --> 00:09:34.706 have more and more lymphocytes.

NOTE Confidence: 0.798355488695652

00:09:34.710 --> 00:09:37.176 So for example in the blue,

NOTE Confidence: 0.798355488695652

00:09:37.180 --> 00:09:39.940 so the square or highlighted

NOTE Confidence: 0.798355488695652

00:09:39.940 --> 00:09:42.700 area and ER positive disease,

NOTE Confidence: 0.798355488695652

00:09:42.700 --> 00:09:43.660 we know lymphocytes,

NOTE Confidence: 0.798355488695652

00:09:43.660 --> 00:09:45.477 it's a very small 6% PCR.

NOTE Confidence: 0.798355488695652

00:09:45.477 --> 00:09:46.996 If you have a lot of lymphocytes,

NOTE Confidence: 0.798355488695652

00:09:47.000 --> 00:09:49.922 it goes up to a respectable 23% and you see

NOTE Confidence: 0.798355488695652

00:09:49.922 --> 00:09:52.480 this same trend across all the subtypes.

NOTE Confidence: 0.798355488695652

00:09:52.480 --> 00:09:53.698 So of course these observations lead

NOTE Confidence: 0.798355488695652

00:09:53.698 --> 00:09:55.440 to a lot of other questions then.

NOTE Confidence: 0.798355488695652

00:09:55.440 --> 00:09:57.484 So why some breast cancers are immune,

NOTE Confidence: 0.798355488695652

00:09:57.490 --> 00:09:59.335 originalists don't is the immune

NOTE Confidence: 0.798355488695652

00:09:59.335 --> 00:10:00.442 microenvironment differ between

NOTE Confidence: 0.798355488695652

00:10:00.442 --> 00:10:02.250 the primary system and the maths,

NOTE Confidence: 0.798355488695652

00:10:02.250 --> 00:10:05.373 it's a different by ER subtype or by race?

NOTE Confidence: 0.798355488695652

00:10:05.380 --> 00:10:07.240 And ultimately the the most important

NOTE Confidence: 0.798355488695652

00:10:07.240 --> 00:10:09.324 question is this a causal relationship

NOTE Confidence: 0.798355488695652

00:10:09.324 --> 00:10:11.682 or immune cell presence is actually

NOTE Confidence: 0.798355488695652

00:10:11.682 --> 00:10:13.811 responsible for the good outcome or

NOTE Confidence: 0.798355488695652

00:10:13.811 --> 00:10:15.737 it's just an association that reflects

NOTE Confidence: 0.798355488695652

00:10:15.740 --> 00:10:17.244 some other underlying biology.

NOTE Confidence: 0.798355488695652

00:10:17.244 --> 00:10:19.500 So when these papers were published,

NOTE Confidence: 0.798355488695652

00:10:19.500 --> 00:10:21.089 you couldn't really test this in people,

NOTE Confidence: 0.798355488695652

00:10:21.090 --> 00:10:22.550 there were no chemotherapy drugs.

NOTE Confidence: 0.798355488695652

00:10:22.550 --> 00:10:24.414 But now we have and we actually have

NOTE Confidence: 0.798355488695652

00:10:24.414 --> 00:10:26.118 the answer to most of these and I

NOTE Confidence: 0.798355488695652

00:10:26.118 --> 00:10:27.631 put there some of the publications

NOTE Confidence: 0.798355488695652

00:10:27.631 --> 00:10:29.635 that that address these these issues.

NOTE Confidence: 0.870431012333333

00:10:31.880 --> 00:10:34.283 So I want to share with you some results

NOTE Confidence: 0.870431012333333

00:10:34.283 --> 00:10:36.645 which I think really informed a lot of

NOTE Confidence: 0.870431012333333

00:10:36.645 --> 00:10:38.887 my thinking about the the value of the

NOTE Confidence: 0.870431012333333

00:10:38.887 --> 00:10:40.996 role of immune system in breast cancer.

NOTE Confidence: 0.870431012333333

00:10:40.996 --> 00:10:43.782 So a few years ago Anton Sofronoff

NOTE Confidence: 0.870431012333333

00:10:43.782 --> 00:10:46.508 was a medical student here at. Yeah.

NOTE Confidence: 0.870431012333333

00:10:46.508 --> 00:10:48.594 At that time took on this project,

NOTE Confidence: 0.870431012333333

00:10:48.600 --> 00:10:51.232 but downloaded all the CG data or an

NOTE Confidence: 0.870431012333333

00:10:51.232 --> 00:10:53.664 AC DNA copy number, mutation data,

NOTE Confidence: 0.870431012333333

00:10:53.664 --> 00:10:55.986 germline snips and ask this question.

NOTE Confidence: 0.870431012333333

00:10:55.990 --> 00:10:57.880 So what drives the immune infiltration

NOTE Confidence: 0.870431012333333

00:10:57.880 --> 00:10:58.825 and breast cancers?

NOTE Confidence: 0.870431012333333

00:10:58.830 --> 00:11:00.810 So we looked at Chrono Heterogeneity,

NOTE Confidence: 0.870431012333333

00:11:00.810 --> 00:11:02.510 mutation load, new antigen load,

NOTE Confidence: 0.870431012333333

00:11:02.510 --> 00:11:04.016 copy number variations,

NOTE Confidence: 0.870431012333333

00:11:04.016 --> 00:11:05.020 germline snips,

NOTE Confidence: 0.870431012333333

00:11:05.020 --> 00:11:07.068 single gene somatic mutations,

NOTE Confidence: 0.870431012333333

00:11:07.068 --> 00:11:08.604 pathway level abnormalities,

NOTE Confidence: 0.870431012333333

00:11:08.610 --> 00:11:10.740 which of these is associated with

NOTE Confidence: 0.870431012333333

00:11:10.740 --> 00:11:11.805 high immune presence,

NOTE Confidence: 0.870431012333333

00:11:11.810 --> 00:11:13.250 whether you think the results showed?

NOTE Confidence: 0.88883495

00:11:15.410 --> 00:11:17.520 So. Gosh.

NOTE Confidence: 0.798638677142857

00:11:22.470 --> 00:11:24.755 So the results are actually

NOTE Confidence: 0.798638677142857

00:11:24.755 --> 00:11:25.669 quite counterintuitive.

NOTE Confidence: 0.798638677142857

00:11:25.670 --> 00:11:27.742 So what this shows you is a correlation

NOTE Confidence: 0.798638677142857

00:11:27.742 --> 00:11:29.446 matrix of about 12 immune gene

NOTE Confidence: 0.798638677142857

00:11:29.446 --> 00:11:31.472 signatures that we use to define the

NOTE Confidence: 0.798638677142857

00:11:31.472 --> 00:11:33.474 immune presence or absence or in your

NOTE Confidence: 0.798638677142857

00:11:33.474 --> 00:11:35.626 richness and about 6 genomic features.

NOTE Confidence: 0.798638677142857

00:11:35.626 --> 00:11:38.519 So the darker brown shows a higher

NOTE Confidence: 0.798638677142857

00:11:38.519 --> 00:11:40.784 correlation value and the darker

NOTE Confidence: 0.798638677142857

00:11:40.784 --> 00:11:43.570 blue shows a negative correlation.

NOTE Confidence: 0.798638677142857

00:11:43.570 --> 00:11:45.292 And you see right away that

NOTE Confidence: 0.798638677142857

00:11:45.292 --> 00:11:46.861 the immune gene signatures are

NOTE Confidence: 0.798638677142857

00:11:46.861 --> 00:11:48.309 highly correlated one another,

NOTE Confidence: 0.798638677142857

00:11:48.310 --> 00:11:49.375 whereas they are not correlated

NOTE Confidence: 0.798638677142857

00:11:49.375 --> 00:11:50.728 very closely at all. In fact,

NOTE Confidence: 0.798638677142857

00:11:50.728 --> 00:11:52.720 they are anti correlated with many of the.

NOTE Confidence: 0.798638677142857

00:11:52.720 --> 00:11:53.404 Economic features.

NOTE Confidence: 0.798638677142857

00:11:53.404 --> 00:11:55.798 So and you see this across the

NOTE Confidence: 0.798638677142857

00:11:55.798 --> 00:11:57.830 board in all the three subtypes.

NOTE Confidence: 0.798638677142857

00:11:57.830 --> 00:12:00.504 So in in primary breast cancer greater

NOTE Confidence: 0.798638677142857

00:12:00.504 --> 00:12:02.550 chromo heterogeneity and higher mutation

NOTE Confidence: 0.798638677142857

00:12:02.550 --> 00:12:04.640 and neoantigen loads are associated

NOTE Confidence: 0.798638677142857

00:12:04.640 --> 00:12:06.750 with lower immune infiltration.

NOTE Confidence: 0.798638677142857

00:12:06.750 --> 00:12:08.486 So there was such a weird finding

NOTE Confidence: 0.798638677142857

00:12:08.486 --> 00:12:10.090 that we actually teamed up with

NOTE Confidence: 0.798638677142857

00:12:10.090 --> 00:12:11.710 with the A colleague from Germany,

NOTE Confidence: 0.798638677142857

00:12:11.710 --> 00:12:14.338 Thomas Cohn to really confirm this

NOTE Confidence: 0.798638677142857

00:12:14.338 --> 00:12:17.250 in an independent data set data sets

NOTE Confidence: 0.798638677142857

00:12:17.250 --> 00:12:20.225 and we find the same same result.

NOTE Confidence: 0.798638677142857

00:12:20.230 --> 00:12:22.790 So why is this interesting?

NOTE Confidence: 0.798638677142857

00:12:22.790 --> 00:12:24.995 Because even though we found no share

NOTE Confidence: 0.798638677142857

00:12:24.995 --> 00:12:26.679 genomic alterations that drive the

NOTE Confidence: 0.798638677142857

00:12:26.679 --> 00:12:28.384 immune infiltration in breast cancer,

NOTE Confidence: 0.798638677142857

00:12:28.390 --> 00:12:30.406 we really find a strong supportive

NOTE Confidence: 0.798638677142857

00:12:30.406 --> 00:12:32.523 evidence that there is an active

NOTE Confidence: 0.798638677142857

00:12:32.523 --> 00:12:34.647 immune editing in early stage disease,

NOTE Confidence: 0.798638677142857

00:12:34.650 --> 00:12:34.962 right.

NOTE Confidence: 0.798638677142857

00:12:34.962 --> 00:12:37.458 So a lot of immune cells in actually

NOTE Confidence: 0.798638677142857

00:12:37.458 --> 00:12:38.995 called remove chromo heterogeneity

NOTE Confidence: 0.798638677142857

00:12:38.995 --> 00:12:41.704 and that's why you have a chromoly

NOTE Confidence: 0.798638677142857

00:12:41.767 --> 00:12:43.975 simple tumor and actually a lower

NOTE Confidence: 0.798638677142857

00:12:43.975 --> 00:12:45.982 your antigen load because the cancer

NOTE Confidence: 0.798638677142857

00:12:45.982 --> 00:12:47.578 cells with the high neoantigen load

NOTE Confidence: 0.798638677142857

00:12:47.578 --> 00:12:49.128 are removed by the immune system.

NOTE Confidence: 0.798638677142857

00:12:49.130 --> 00:12:51.230 So that's really attractive.

NOTE Confidence: 0.798638677142857

00:12:51.230 --> 00:12:54.380 Hypothesis and it makes testable predictions.

NOTE Confidence: 0.798638677142857

00:12:54.380 --> 00:12:56.980 So one prediction is that even tumor cells

NOTE Confidence: 0.798638677142857

00:12:56.980 --> 00:12:59.720 sort of undergo medical transformation.

NOTE Confidence: 0.798638677142857

00:12:59.720 --> 00:13:01.340 Some of it could be eliminated

NOTE Confidence: 0.798638677142857

00:13:01.340 --> 00:13:02.420 by the immune system.

NOTE Confidence: 0.798638677142857

00:13:02.420 --> 00:13:03.460 So if that's really true,

NOTE Confidence: 0.798638677142857

00:13:03.460 --> 00:13:05.100 then then actually immunotherapy

NOTE Confidence: 0.798638677142857

00:13:05.100 --> 00:13:06.740 should work as chemoprevention.

NOTE Confidence: 0.798638677142857

00:13:06.740 --> 00:13:08.316 Of course, it's too toxic to do that,

NOTE Confidence: 0.798638677142857

00:13:08.320 --> 00:13:09.900 but the concept is important.

NOTE Confidence: 0.798638677142857

00:13:09.900 --> 00:13:11.867 So we're going to test this in

NOTE Confidence: 0.798638677142857

00:13:11.867 --> 00:13:13.651 an ongoing large event trial that

NOTE Confidence: 0.798638677142857

00:13:13.651 --> 00:13:15.702 uses symbolism for a year to see

NOTE Confidence: 0.798638677142857

00:13:15.763 --> 00:13:17.171 whether it alters contralateral

NOTE Confidence: 0.798638677142857

00:13:17.171 --> 00:13:19.126 breast cancer events and also

NOTE Confidence: 0.798638677142857

00:13:19.126 --> 00:13:21.210 whether it alters breast density.

NOTE Confidence: 0.798638677142857

00:13:21.210 --> 00:13:23.862 Which is sort of a somewhat

NOTE Confidence: 0.798638677142857

00:13:23.862 --> 00:13:25.188 validated risk predictor.

NOTE Confidence: 0.798638677142857

00:13:25.190 --> 00:13:26.961 But the most important consequence is this

NOTE Confidence: 0.798638677142857

00:13:26.961 --> 00:13:29.239 that when we actually diagnose these cancers,

NOTE Confidence: 0.798638677142857

00:13:29.240 --> 00:13:31.508 there may be a quasi equilibrium fight

NOTE Confidence: 0.798638677142857

00:13:31.508 --> 00:13:33.787 between the immune system and the cancer.

NOTE Confidence: 0.798638677142857

00:13:33.790 --> 00:13:35.446 So when there are a lot of immune cells,

NOTE Confidence: 0.798638677142857

00:13:35.450 --> 00:13:37.352 it's kind of indicate that the

NOTE Confidence: 0.798638677142857

00:13:37.352 --> 00:13:39.367 immune system is having almost upper

NOTE Confidence: 0.798638677142857

00:13:39.367 --> 00:13:41.754 hand and that's why it actually is

NOTE Confidence: 0.798638677142857

00:13:41.754 --> 00:13:43.449 associated with better prognosis.

NOTE Confidence: 0.798638677142857

00:13:43.450 --> 00:13:45.284 But at that stage you might actually

NOTE Confidence: 0.798638677142857

00:13:45.284 --> 00:13:47.127 help tip the balance towards the

NOTE Confidence: 0.798638677142857

00:13:47.127 --> 00:13:49.119 immune system by chemotherapy or by

NOTE Confidence: 0.798638677142857

00:13:49.119 --> 00:13:51.168 immune checkpoint inhibitors and then.

NOTE Confidence: 0.798638677142857

00:13:51.170 --> 00:13:52.874 Do not have the drugs to test this.

NOTE Confidence: 0.798638677142857

00:13:52.880 --> 00:13:54.434 And we actually launched 4 studies

NOTE Confidence: 0.798638677142857

00:13:54.434 --> 00:13:55.802 to to address these questions

NOTE Confidence: 0.798638677142857

00:13:55.802 --> 00:13:57.488 and three of them have results,

NOTE Confidence: 0.798638677142857

00:13:57.490 --> 00:13:58.816 and I'll show that to you.

NOTE Confidence: 0.798638677142857

00:13:58.820 --> 00:14:01.494 But the third prediction is also interesting,

NOTE Confidence: 0.798638677142857

00:14:01.500 --> 00:14:01.850 right?

NOTE Confidence: 0.798638677142857

00:14:01.850 --> 00:14:04.300 So if you really follow this logic,

NOTE Confidence: 0.798638677142857

00:14:04.300 --> 00:14:05.940 then the metastatic disease should

NOTE Confidence: 0.798638677142857

00:14:05.940 --> 00:14:07.980 really arrive through an immune escape.

NOTE Confidence: 0.798638677142857

00:14:07.980 --> 00:14:09.835 So we did a series of studies

NOTE Confidence: 0.798638677142857

00:14:09.835 --> 00:14:10.630 to compare primary

NOTE Confidence: 0.790063143846154

00:14:10.694 --> 00:14:12.612 exams and maths, and it's among the

NOTE Confidence: 0.790063143846154

00:14:12.612 --> 00:14:14.160 first groups to show that actually

NOTE Confidence: 0.790063143846154

00:14:14.214 --> 00:14:16.314 metastatic lesions in breast cancer

NOTE Confidence: 0.790063143846154

00:14:16.314 --> 00:14:17.574 are profoundly immunocompromised.

NOTE Confidence: 0.790063143846154

00:14:17.580 --> 00:14:20.562 And we also looked at whether there

NOTE Confidence: 0.790063143846154

00:14:20.562 --> 00:14:22.610 is subtle variations by sight.

NOTE Confidence: 0.790063143846154

00:14:22.610 --> 00:14:24.668 So now these are all sort of

NOTE Confidence: 0.790063143846154

00:14:24.670 --> 00:14:26.306 relatively valid accepted principles.

NOTE Confidence: 0.790063143846154

00:14:26.306 --> 00:14:29.289 I I thought I showed this to you,

NOTE Confidence: 0.790063143846154

00:14:29.290 --> 00:14:30.780 especially for those of you

NOTE Confidence: 0.790063143846154

00:14:30.780 --> 00:14:31.972 who are younger investigators.

NOTE Confidence: 0.790063143846154

00:14:31.980 --> 00:14:33.932 So there are risks of being coming up

NOTE Confidence: 0.790063143846154

00:14:33.932 --> 00:14:35.939 with an idea too early or too late.

NOTE Confidence: 0.790063143846154

00:14:35.940 --> 00:14:37.010 So this particular idea came

NOTE Confidence: 0.790063143846154

00:14:37.010 --> 00:14:38.400 on a little bit too early.

NOTE Confidence: 0.790063143846154

00:14:38.400 --> 00:14:40.740 In 2012, about a month of Tiki came here.

NOTE Confidence: 0.790063143846154

00:14:40.740 --> 00:14:43.372 I approached Merck to do 2 large

NOTE Confidence: 0.790063143846154

00:14:43.372 --> 00:14:45.940 studies in the curative setting.

NOTE Confidence: 0.790063143846154

00:14:45.940 --> 00:14:47.676 What was the neoadjuvant trial to see

NOTE Confidence: 0.790063143846154

00:14:47.676 --> 00:14:49.477 whether we could actually push the PCR?

NOTE Confidence: 0.790063143846154

00:14:49.480 --> 00:14:51.216 It's up based on the associations that

NOTE Confidence: 0.790063143846154

00:14:51.216 --> 00:14:53.078 I showed you to test the causality.

NOTE Confidence: 0.790063143846154

00:14:53.080 --> 00:14:54.354 The other one was an adjuvant study.

NOTE Confidence: 0.790063143846154

00:14:54.360 --> 00:14:56.474 We could actually improve the outcome by

NOTE Confidence: 0.790063143846154

00:14:56.474 --> 00:14:58.269 giving people liberalism out and eradicate.

NOTE Confidence: 0.790063143846154

00:14:58.270 --> 00:15:00.230 Micromedex and this is what they said,

NOTE Confidence: 0.790063143846154

00:15:00.230 --> 00:15:02.218 sorry you're unable to avoid the drug

NOTE Confidence: 0.790063143846154

00:15:02.218 --> 00:15:04.365 and the monetary support at this time

NOTE Confidence: 0.790063143846154

00:15:04.365 --> 00:15:06.225 due to unclear regularly path forward.

NOTE Confidence: 0.790063143846154

00:15:06.230 --> 00:15:08.043 But it was three years later they

NOTE Confidence: 0.790063143846154

00:15:08.043 --> 00:15:09.563 actually realized that there is a

NOTE Confidence: 0.790063143846154

00:15:09.563 --> 00:15:10.949 path forward and they actually run

NOTE Confidence: 0.790063143846154

00:15:10.949 --> 00:15:12.554 both of these studies or or agree to

NOTE Confidence: 0.790063143846154

00:15:12.554 --> 00:15:14.790 do it and they to their credit they

NOTE Confidence: 0.790063143846154

00:15:14.790 --> 00:15:16.869 actually invited me back to their

NOTE Confidence: 0.790063143846154

00:15:16.869 --> 00:15:18.975 steering committee of the new adjuvant

NOTE Confidence: 0.790063143846154

00:15:18.975 --> 00:15:21.598 trial and I lead the adjuvant trial.

NOTE Confidence: 0.790063143846154

00:15:21.600 --> 00:15:23.959 So what do these studies show it?

NOTE Confidence: 0.790063143846154

00:15:23.960 --> 00:15:26.270 This is just the selection that is

NOTE Confidence: 0.790063143846154

00:15:26.270 --> 00:15:28.331 representative of the findings from

NOTE Confidence: 0.790063143846154

00:15:28.331 --> 00:15:30.339 the neoadjuvant immunotherapy trials.

NOTE Confidence: 0.790063143846154

00:15:30.340 --> 00:15:32.284 And they were lounged in triple

NOTE Confidence: 0.790063143846154

00:15:32.284 --> 00:15:33.994 negative disease because of the

NOTE Confidence: 0.790063143846154

00:15:33.994 --> 00:15:35.754 really strong association of immune

NOTE Confidence: 0.790063143846154

00:15:35.754 --> 00:15:38.025 cells with pathologic CR or strong

NOTE Confidence: 0.790063143846154

00:15:38.025 --> 00:15:39.637 strong association with prognosis.

NOTE Confidence: 0.790063143846154

00:15:39.640 --> 00:15:41.440 And by and large triple negative

NOTE Confidence: 0.790063143846154

00:15:41.440 --> 00:15:43.638 cancers have a higher in your presence.

NOTE Confidence: 0.790063143846154

00:15:43.640 --> 00:15:45.434 So all these studies took place

NOTE Confidence: 0.790063143846154

00:15:45.434 --> 00:15:47.380 in in that space except one,

NOTE Confidence: 0.790063143846154

00:15:47.380 --> 00:15:48.748 the ice spy all talk to you a

NOTE Confidence: 0.790063143846154

00:15:48.748 --> 00:15:49.739 little bit more about it.

NOTE Confidence: 0.790063143846154

00:15:49.740 --> 00:15:51.324 So what this study shows is that the

NOTE Confidence: 0.790063143846154

00:15:51.324 --> 00:15:52.729 the computer response rates improved.

NOTE Confidence: 0.790063143846154

00:15:52.730 --> 00:15:54.606 Didn't have as much as we thought.

NOTE Confidence: 0.790063143846154

00:15:54.610 --> 00:15:56.666 So the largest study keynote 5 to 2,

NOTE Confidence: 0.790063143846154

00:15:56.670 --> 00:15:58.580 the Merck study showed improvement

NOTE Confidence: 0.790063143846154

00:15:58.580 --> 00:16:00.819 about 7 percent, 56 to 63.

NOTE Confidence: 0.790063143846154

00:16:00.819 --> 00:16:02.271 Really underwhelming because chemotherapy

NOTE Confidence: 0.790063143846154

00:16:02.271 --> 00:16:04.829 trials could do double digit improvements.

NOTE Confidence: 0.790063143846154

00:16:04.830 --> 00:16:06.170 Yet the chemo studies actually

NOTE Confidence: 0.790063143846154

00:16:06.170 --> 00:16:07.510 didn't really improve the event

NOTE Confidence: 0.790063143846154

00:16:07.562 --> 00:16:08.950 free survival that dramatically.

NOTE Confidence: 0.790063143846154

00:16:08.950 --> 00:16:10.055 Oftentimes it didn't deal with

NOTE Confidence: 0.790063143846154

00:16:10.055 --> 00:16:11.490 it all to a significant extent.

NOTE Confidence: 0.790063143846154

00:16:11.490 --> 00:16:12.510 But keynote 522 did.

NOTE Confidence: 0.790063143846154

00:16:12.510 --> 00:16:15.230 You see the same in an even smaller study,

NOTE Confidence: 0.790063143846154

00:16:15.230 --> 00:16:15.556 paranormal.

NOTE Confidence: 0.790063143846154

00:16:15.556 --> 00:16:18.480 They're also showed a 9% even PCR rate.

NOTE Confidence: 0.790063143846154

00:16:18.480 --> 00:16:19.770 Not even significant,

NOTE Confidence: 0.790063143846154

00:16:19.770 --> 00:16:22.227 but the event free survival was significant.

NOTE Confidence: 0.790063143846154

00:16:22.230 --> 00:16:22.958 The other?

NOTE Confidence: 0.790063143846154

00:16:22.958 --> 00:16:25.142 Important finding in this sort of

NOTE Confidence: 0.790063143846154

00:16:25.142 --> 00:16:27.069 or observation from these studies

NOTE Confidence: 0.790063143846154

00:16:27.069 --> 00:16:28.959 is that in metastatic disease,

NOTE Confidence: 0.790063143846154

00:16:28.960 --> 00:16:30.900 again parallelism have improved the

NOTE Confidence: 0.790063143846154

00:16:30.900 --> 00:16:32.840 outcome when combined with chemotherapy.

NOTE Confidence: 0.790063143846154

00:16:32.840 --> 00:16:34.696 But this was only seen in the pediatric

NOTE Confidence: 0.790063143846154

00:16:34.696 --> 00:16:35.980 and positive patients whereas in

NOTE Confidence: 0.790063143846154

00:16:35.980 --> 00:16:37.528 the early stage setting you don't

NOTE Confidence: 0.790063143846154

00:16:37.528 --> 00:16:38.999 need to have Pedialyte and one.

NOTE Confidence: 0.790063143846154

00:16:39.000 --> 00:16:40.596 So that confuses a lot of people.

NOTE Confidence: 0.790063143846154

00:16:40.600 --> 00:16:42.182 But I think there is a really

NOTE Confidence: 0.790063143846154

00:16:42.182 --> 00:16:42.860 simple and elegant

NOTE Confidence: 0.866753938666667

00:16:42.915 --> 00:16:44.415 explanation and it comes from the

NOTE Confidence: 0.866753938666667

00:16:44.415 --> 00:16:46.032 slide that I showed you previously

NOTE Confidence: 0.866753938666667

00:16:46.032 --> 00:16:47.730 from the fact that the metastatic

NOTE Confidence: 0.866753938666667

00:16:47.730 --> 00:16:50.253 lesions are immunocompromised or really

NOTE Confidence: 0.866753938666667

00:16:50.253 --> 00:16:52.857 immunosuppressed immune attenuated so.

NOTE Confidence: 0.866753938666667

00:16:52.860 --> 00:16:54.396 And the only stage setting I think a

NOTE Confidence: 0.866753938666667

00:16:54.396 --> 00:16:55.676 small amount of immune presence that

NOTE Confidence: 0.866753938666667

00:16:55.676 --> 00:16:57.474 you could miss with the biopsy and they

NOTE Confidence: 0.866753938666667

00:16:57.474 --> 00:16:58.920 actually miss it oftentimes with biopsy.

NOTE Confidence: 0.866753938666667

00:16:58.920 --> 00:17:00.704 So this is a work that Adriana Khan,

NOTE Confidence: 0.866753938666667

00:17:00.710 --> 00:17:02.926 one of our fellows showed and we presented

NOTE Confidence: 0.866753938666667

00:17:02.926 --> 00:17:05.207 the San Antonio Breast Cancer meeting.

NOTE Confidence: 0.866753938666667

00:17:05.210 --> 00:17:07.235 So even a few period like in one positive

NOTE Confidence: 0.866753938666667

00:17:07.235 --> 00:17:08.981 cells that are intermixed with the

NOTE Confidence: 0.866753938666667

00:17:08.981 --> 00:17:10.778 micro environment and missed the initial

NOTE Confidence: 0.866753938666667

00:17:10.778 --> 00:17:12.476 biopsy could be enough to actually

NOTE Confidence: 0.866753938666667

00:17:12.476 --> 00:17:14.794 ignite an immune response and the same

NOTE Confidence: 0.866753938666667

00:17:14.794 --> 00:17:16.990 way chemotherapy ignites sort of like

NOTE Confidence: 0.866753938666667

00:17:17.061 --> 00:17:19.609 one expression in the more massive scale,

NOTE Confidence: 0.866753938666667

00:17:19.610 --> 00:17:21.479 but you don't see the same thing

NOTE Confidence: 0.866753938666667

00:17:21.479 --> 00:17:23.850 in in in the metastatic setting.

NOTE Confidence: 0.866753938666667

00:17:23.850 --> 00:17:26.510 So the other question was this really.

NOTE Confidence: 0.866753938666667

00:17:26.510 --> 00:17:29.042 This thing observation that why small

NOTE Confidence: 0.866753938666667

00:17:29.042 --> 00:17:31.584 improvements in Pathologic CR really lead

NOTE Confidence: 0.866753938666667

00:17:31.584 --> 00:17:33.930 to large improvements in survival whereas

NOTE Confidence: 0.866753938666667

00:17:33.930 --> 00:17:36.419 in other setting it doesn't happen.

NOTE Confidence: 0.866753938666667

00:17:36.420 --> 00:17:38.275 So that brings me to another sort

NOTE Confidence: 0.866753938666667

00:17:38.275 --> 00:17:40.280 of debate that used to rage and

NOTE Confidence: 0.866753938666667

00:17:40.280 --> 00:17:42.002 the the breast cancer community and

NOTE Confidence: 0.866753938666667

00:17:42.065 --> 00:17:43.665 we spent a lot of time on it.

NOTE Confidence: 0.866753938666667

00:17:43.670 --> 00:17:45.548 It's really prompted by the 1st

NOTE Confidence: 0.866753938666667

00:17:45.548 --> 00:17:47.444 initial new adjuvant trials and shovel

NOTE Confidence: 0.866753938666667

00:17:47.444 --> 00:17:49.196 power to show improvement in PCR,

NOTE Confidence: 0.866753938666667

00:17:49.200 --> 00:17:50.970 but was woefully underpowered and

NOTE Confidence: 0.866753938666667

00:17:50.970 --> 00:17:53.224 included all subtypes to to really

NOTE Confidence: 0.866753938666667

00:17:53.224 --> 00:17:54.896 show improvement in survival.

NOTE Confidence: 0.866753938666667

00:17:54.900 --> 00:17:56.937 So this matter analysis by the FDA

NOTE Confidence: 0.866753938666667

00:17:56.937 --> 00:17:58.939 and showed very little in fact

NOTE Confidence: 0.866753938666667

00:17:58.939 --> 00:18:00.714 no relationships at all between

NOTE Confidence: 0.866753938666667

00:18:00.714 --> 00:18:02.479 improvement in PCR and survival.

NOTE Confidence: 0.866753938666667

00:18:02.480 --> 00:18:04.118 They confused a lot of people,

NOTE Confidence: 0.866753938666667

00:18:04.120 --> 00:18:05.751 but it would have to fly against

NOTE Confidence: 0.866753938666667

00:18:05.751 --> 00:18:06.770 the totally common sense.

NOTE Confidence: 0.866753938666667

00:18:06.770 --> 00:18:09.042 Observations, Taxol improved pathologic,

NOTE Confidence: 0.866753938666667

00:18:09.042 --> 00:18:11.314 sciarid improved survival receptive

NOTE Confidence: 0.866753938666667

00:18:11.314 --> 00:18:12.690 improved Pathologic CR,

NOTE Confidence: 0.866753938666667

00:18:12.690 --> 00:18:13.740 it improves survival.

NOTE Confidence: 0.866753938666667

00:18:13.740 --> 00:18:15.140 Platinum improved Pathologic CR

NOTE Confidence: 0.866753938666667

00:18:15.140 --> 00:18:17.355 it's and now we know that it

NOTE Confidence: 0.866753938666667

00:18:17.355 --> 00:18:18.467 improves survival as well.

NOTE Confidence: 0.866753938666667

00:18:18.470 --> 00:18:20.624 And of course the immune checkpoint

NOTE Confidence: 0.866753938666667

00:18:20.624 --> 00:18:21.701 inhibitors improved pathologic

NOTE Confidence: 0.866753938666667

00:18:21.701 --> 00:18:22.929 security improve survival.

NOTE Confidence: 0.866753938666667

00:18:22.930 --> 00:18:24.740 But nevertheless it's really true

NOTE Confidence: 0.866753938666667

00:18:24.740 --> 00:18:26.991 that at the individual trial level

NOTE Confidence: 0.866753938666667

00:18:26.991 --> 00:18:28.886 the relationship between the PCR

NOTE Confidence: 0.866753938666667

00:18:28.886 --> 00:18:30.839 change improvement and the improvement

NOTE Confidence: 0.866753938666667

00:18:30.839 --> 00:18:32.689 in PFS is hugely variable.

NOTE Confidence: 0.866753938666667

00:18:32.690 --> 00:18:34.028 So that's the next question to

NOTE Confidence: 0.866753938666667

00:18:34.028 --> 00:18:35.823 study why and I actually have a

NOTE Confidence: 0.866753938666667

00:18:35.823 --> 00:18:36.959 good explanation for you.

NOTE Confidence: 0.866753938666667

00:18:36.960 --> 00:18:39.024 And I think it's very elegant and simple.

NOTE Confidence: 0.866753938666667

00:18:39.030 --> 00:18:41.598 But to understand that you need

NOTE Confidence: 0.866753938666667

00:18:41.598 --> 00:18:43.754 to familiarize yourself with this

NOTE Confidence: 0.866753938666667

00:18:43.754 --> 00:18:46.351 concept of of a continuous metric of

NOTE Confidence: 0.866753938666667

00:18:46.351 --> 00:18:48.948 of outcome or pathological response.

NOTE Confidence: 0.866753938666667

00:18:48.950 --> 00:18:51.939 So again in 2007 we developed this

NOTE Confidence: 0.866753938666667

00:18:51.939 --> 00:18:54.250 metric called residual cancer burden

NOTE Confidence: 0.866753938666667

00:18:54.250 --> 00:18:56.615 to capture the pathological residual

NOTE Confidence: 0.866753938666667

00:18:56.615 --> 00:18:59.609 disease as a continuous variable.

NOTE Confidence: 0.866753938666667

00:18:59.610 --> 00:19:01.370 We did that because continuous

NOTE Confidence: 0.866753938666667

00:19:01.370 --> 00:19:03.130 variables are more powerful to

NOTE Confidence: 0.866753938666667

00:19:03.188 --> 00:19:05.360 identify genes that would be associated

NOTE Confidence: 0.866753938666667

00:19:05.360 --> 00:19:07.070 with outcome or not but.

NOTE Confidence: 0.866753938666667

00:19:07.070 --> 00:19:08.876 So eventually it took sort of

NOTE Confidence: 0.866753938666667

00:19:08.876 --> 00:19:10.990 traction in the form of categories,

NOTE Confidence: 0.866753938666667

00:19:10.990 --> 00:19:13.678 so you can use this continuous score to

NOTE Confidence: 0.866753938666667

00:19:13.678 --> 00:19:17.258 create bins of 0 being complete response.

NOTE Confidence: 0.866753938666667

00:19:17.260 --> 00:19:17.898 Another bin.

NOTE Confidence: 0.866753938666667

00:19:17.898 --> 00:19:19.493 That's the minimal residual disease

NOTE Confidence: 0.866753938666667

00:19:19.493 --> 00:19:21.578 or RCB 1 moderate amount or CB2

NOTE Confidence: 0.866753938666667

00:19:21.578 --> 00:19:23.360 and a large amount of RCB 3.

NOTE Confidence: 0.866753938666667

00:19:23.360 --> 00:19:25.720 But the truth is that this is really

NOTE Confidence: 0.866753938666667

00:19:25.720 --> 00:19:27.161 a continuous scroll and that's

NOTE Confidence: 0.866753938666667

00:19:27.161 --> 00:19:28.476 why we did it so.

NOTE Confidence: 0.866753938666667

00:19:28.480 --> 00:19:31.168 Be teamed up the deal I spoke

NOTE Confidence: 0.866753938666667

00:19:31.168 --> 00:19:32.320 to investigators because

NOTE Confidence: 0.683619764

00:19:32.395 --> 00:19:34.530 this continuous sort of score,

NOTE Confidence: 0.683619764

00:19:34.530 --> 00:19:36.175 I thought actually could reveal

NOTE Confidence: 0.683619764

00:19:36.175 --> 00:19:37.491 some really interesting things

NOTE Confidence: 0.683619764

00:19:37.491 --> 00:19:39.078 about how different drugs work.

NOTE Confidence: 0.683619764

00:19:39.080 --> 00:19:41.969 So what you see here is actually a pretty

NOTE Confidence: 0.683619764

00:19:41.969 --> 00:19:45.299 cool picture of the continuous RCB scores in

NOTE Confidence: 0.683619764

00:19:45.299 --> 00:19:48.097 seven different arms of the eye spy study.

NOTE Confidence: 0.683619764

00:19:48.100 --> 00:19:49.745 So the eye spy is randomized trials,

NOTE Confidence: 0.683619764

00:19:49.750 --> 00:19:51.955 the control arm is always staxel ACC,

NOTE Confidence: 0.683619764

00:19:51.960 --> 00:19:55.434 and but you see here is the RCB values

NOTE Confidence: 0.683619764

00:19:55.434 --> 00:19:57.664 from zero to 50 is complete response.

NOTE Confidence: 0.683619764

00:19:57.664 --> 00:19:58.507 Five is expensive.

NOTE Confidence: 0.683619764

00:19:58.510 --> 00:19:59.050 Single disease.

NOTE Confidence: 0.683619764

00:19:59.050 --> 00:20:01.210 This kind of shows you the the the

NOTE Confidence: 0.683619764

00:20:01.272 --> 00:20:03.120 prevalence of the density or the

NOTE Confidence: 0.683619764

00:20:03.120 --> 00:20:05.012 frequency with which you encounter a

NOTE Confidence: 0.683619764

00:20:05.012 --> 00:20:07.112 particular RCB value in the trial arm.

NOTE Confidence: 0.683619764

00:20:07.120 --> 00:20:10.552 So the black is the control and the dotted

NOTE Confidence: 0.683619764

00:20:10.552 --> 00:20:11.992 lines are various experimental drugs.

NOTE Confidence: 0.683619764

00:20:12.000 --> 00:20:15.168 I just want to look at you the two

NOTE Confidence: 0.683619764

00:20:15.168 --> 00:20:18.370 panels which are labeled so I don't

NOTE Confidence: 0.683619764

00:20:18.370 --> 00:20:20.819 think I can use a A.

NOTE Confidence: 0.683619764

00:20:20.820 --> 00:20:21.676 Sort of a pointer,

NOTE Confidence: 0.683619764

00:20:21.676 --> 00:20:22.746 but you probably see there

NOTE Confidence: 0.683619764

00:20:22.746 --> 00:20:23.739 that the bottom panel,

NOTE Confidence: 0.683619764

00:20:23.740 --> 00:20:25.068 which is regimen 7,

NOTE Confidence: 0.683619764

00:20:25.068 --> 00:20:27.780 you have a large improvement in PCR rates,

NOTE Confidence: 0.683619764

00:20:27.780 --> 00:20:29.440 right, because the the initial

NOTE Confidence: 0.683619764

00:20:29.440 --> 00:20:31.100 zero values are much higher.

NOTE Confidence: 0.683619764

00:20:31.100 --> 00:20:32.820 That's where the curves start.

NOTE Confidence: 0.683619764

00:20:32.820 --> 00:20:35.060 But you also see a massive shift towards

NOTE Confidence: 0.683619764

00:20:35.060 --> 00:20:36.979 the smaller values across the board.

NOTE Confidence: 0.683619764

00:20:36.980 --> 00:20:39.338 If you look at the Regiment 3 on the

NOTE Confidence: 0.683619764

00:20:39.338 --> 00:20:41.579 top instead of right hand corner,

NOTE Confidence: 0.683619764

00:20:41.580 --> 00:20:43.260 then you see that that regimen

NOTE Confidence: 0.683619764

00:20:43.260 --> 00:20:44.380 also improves PCR rates.

NOTE Confidence: 0.683619764

00:20:44.380 --> 00:20:47.035 But it does it by moving the RCB 1,

NOTE Confidence: 0.683619764

00:20:47.040 --> 00:20:49.460 the little residual disease group,

NOTE Confidence: 0.683619764

00:20:49.460 --> 00:20:51.720 into the PCR company response.

NOTE Confidence: 0.683619764

00:20:51.720 --> 00:20:53.424 And that is very unlikely to

NOTE Confidence: 0.683619764

00:20:53.424 --> 00:20:55.060 affect survival like it doesn't.

NOTE Confidence: 0.683619764

00:20:55.060 --> 00:20:56.465 But this particular regimen didn't

NOTE Confidence: 0.683619764

00:20:56.465 --> 00:20:58.680 affect at all the higher residual cancer.

NOTE Confidence: 0.683619764

00:20:58.680 --> 00:21:01.116 So we thought that actually measuring

NOTE Confidence: 0.683619764

00:21:01.116 --> 00:21:03.689 the the distribution of the differences

NOTE Confidence: 0.683619764

00:21:03.689 --> 00:21:06.323 in residual cancer burden scores could

NOTE Confidence: 0.683619764

00:21:06.323 --> 00:21:08.738 capture the efficacy of a regimen.

NOTE Confidence: 0.683619764

00:21:08.740 --> 00:21:10.406 And we developed a new statistical tool

NOTE Confidence: 0.683619764

00:21:10.406 --> 00:21:12.196 that you can find in this paper and

NOTE Confidence: 0.683619764

00:21:12.196 --> 00:21:14.056 you can even play with it if you have

NOTE Confidence: 0.683619764

00:21:14.056 --> 00:21:15.601 a breast cancer on this open website,

NOTE Confidence: 0.683619764

00:21:15.601 --> 00:21:17.406 we call it treatment efficacy

NOTE Confidence: 0.683619764

00:21:17.406 --> 00:21:19.305 score and it basically compares

NOTE Confidence: 0.683619764

00:21:19.305 --> 00:21:21.275 the distribution of RCB scores.

NOTE Confidence: 0.683619764

00:21:21.280 --> 00:21:23.440 Cross through trial arms in that

NOTE Confidence: 0.683619764

00:21:23.440 --> 00:21:24.880 particular metric actually really

NOTE Confidence: 0.683619764

00:21:24.940 --> 00:21:26.575 correlates quite well with event

NOTE Confidence: 0.683619764

00:21:26.575 --> 00:21:28.709 free survival which is what you see.

NOTE Confidence: 0.683619764

00:21:28.710 --> 00:21:29.650 There's a significant difference.

NOTE Confidence: 0.683619764

00:21:29.650 --> 00:21:31.530 There is an event free survival improvement.

NOTE Confidence: 0.683619764

00:21:31.530 --> 00:21:33.220 Is that all significant improvement

NOTE Confidence: 0.683619764

00:21:33.220 --> 00:21:35.763 in this test score then you don't

NOTE Confidence: 0.683619764

00:21:35.763 --> 00:21:36.948 have significant improvement

NOTE Confidence: 0.683619764

00:21:36.948 --> 00:21:38.528 in event free survival.

NOTE Confidence: 0.683619764

00:21:38.530 --> 00:21:40.468 So we're going to validate this

NOTE Confidence: 0.683619764

00:21:40.468 --> 00:21:42.250 within with the other groups.

NOTE Confidence: 0.683619764

00:21:42.250 --> 00:21:44.050 So we're not move to this other question

NOTE Confidence: 0.683619764

00:21:44.050 --> 00:21:45.781 that these studies show up, right.

NOTE Confidence: 0.683619764

00:21:45.781 --> 00:21:48.967 So pembrolizumab is expensive and 15%

NOTE Confidence: 0.683619764

00:21:48.970 --> 00:21:51.028 of the patients have severe toxicity,

NOTE Confidence: 0.683619764

00:21:51.030 --> 00:21:51.442 so.

NOTE Confidence: 0.683619764

00:21:51.442 --> 00:21:54.326 He entered into this race to find

NOTE Confidence: 0.683619764

00:21:54.326 --> 00:21:56.527 predictive markers that define the

NOTE Confidence: 0.683619764

00:21:56.527 --> 00:21:58.697 patients who need pembrolizumab and

NOTE Confidence: 0.683619764

00:21:58.697 --> 00:22:01.579 this is a slide from from us from

NOTE Confidence: 0.683619764

00:22:01.579 --> 00:22:03.392 a group in Germany civil libel.

NOTE Confidence: 0.683619764

00:22:03.392 --> 00:22:05.740 And one of my former lab members Thomas Kuhn,

NOTE Confidence: 0.683619764

00:22:05.740 --> 00:22:08.080 who leads their translational research arm.

NOTE Confidence: 0.683619764

00:22:08.080 --> 00:22:11.083 And what they show in this randomized

NOTE Confidence: 0.683619764

00:22:11.083 --> 00:22:12.746 immunotherapy versus chemotherapy alone

NOTE Confidence: 0.683619764

00:22:12.746 --> 00:22:14.944 ARM study that there are a number

NOTE Confidence: 0.683619764

00:22:14.944 --> 00:22:16.632 of molecular variables that predict

NOTE Confidence: 0.683619764

00:22:16.632 --> 00:22:19.375 response to any if you have them like

NOTE Confidence: 0.683619764

00:22:19.375 --> 00:22:21.865 high commutation burden or a high.

NOTE Confidence: 0.626329596666667

00:22:21.870 --> 00:22:24.294 Energy and expression or high P like in

NOTE Confidence: 0.626329596666667

00:22:24.294 --> 00:22:26.303 one expression or high till comes you

NOTE Confidence: 0.626329596666667

00:22:26.303 --> 00:22:28.440 have higher PCR rate with chemotherapy,

NOTE Confidence: 0.626329596666667

00:22:28.440 --> 00:22:30.232 chemotherapy but also with

NOTE Confidence: 0.626329596666667

00:22:30.232 --> 00:22:31.576 chemotherapy plus immunotherapy.

NOTE Confidence: 0.626329596666667

00:22:31.580 --> 00:22:33.965 But the improvement by immunotherapy

NOTE Confidence: 0.626329596666667

00:22:33.965 --> 00:22:35.873 happens in both groups,

NOTE Confidence: 0.626329596666667

00:22:35.880 --> 00:22:37.580 the remediation low and high,

NOTE Confidence: 0.626329596666667

00:22:37.580 --> 00:22:39.876 the PD low and high or the field

NOTE Confidence: 0.626329596666667

00:22:39.876 --> 00:22:41.619 count low and high groups.

NOTE Confidence: 0.626329596666667

00:22:41.620 --> 00:22:44.042 So these are these one of these

NOTE Confidence: 0.626329596666667

00:22:44.042 --> 00:22:45.936 metrics are selective to identify

NOTE Confidence: 0.626329596666667

00:22:45.936 --> 00:22:47.896 who actually needed the panel,

NOTE Confidence: 0.626329596666667

00:22:47.900 --> 00:22:49.734 but we have an idea who actually

NOTE Confidence: 0.626329596666667

00:22:49.734 --> 00:22:50.880 might benefit from Pedro.

NOTE Confidence: 0.626329596666667

00:22:50.880 --> 00:22:53.218 So we teamed up with the investigators.

NOTE Confidence: 0.626329596666667

00:22:53.220 --> 00:22:55.170 On the build who previously suggested

NOTE Confidence: 0.626329596666667

00:22:55.170 --> 00:22:57.653 that MH subclass 2 expression in tumor

NOTE Confidence: 0.626329596666667

00:22:57.653 --> 00:22:59.897 cells might actually identify a group,

NOTE Confidence: 0.626329596666667

00:22:59.900 --> 00:23:01.340 the group of patients who

NOTE Confidence: 0.626329596666667

00:23:01.340 --> 00:23:02.492 really need it Pembroke.

NOTE Confidence: 0.626329596666667

00:23:02.500 --> 00:23:04.966 So I need to see class to is is

NOTE Confidence: 0.626329596666667

00:23:04.966 --> 00:23:08.000 mostly expressed in immune cells and

NOTE Confidence: 0.626329596666667

00:23:08.000 --> 00:23:10.148 participates in antigen presentation,

NOTE Confidence: 0.626329596666667

00:23:10.150 --> 00:23:12.294 but it can be induced to be expressed

NOTE Confidence: 0.626329596666667

00:23:12.294 --> 00:23:14.426 in cancer cells and epithelial cells

NOTE Confidence: 0.626329596666667

00:23:14.426 --> 00:23:17.089 by interferon gamma, for example, so.

NOTE Confidence: 0.626329596666667

00:23:17.089 --> 00:23:20.107 Have you run this immunity chemistry,

NOTE Confidence: 0.626329596666667

00:23:20.110 --> 00:23:21.990 a simple immunity chemistry for

NOTE Confidence: 0.626329596666667

00:23:21.990 --> 00:23:23.494 emission classical expression on

NOTE Confidence: 0.626329596666667

00:23:23.494 --> 00:23:25.565 cancer as opposed to the immune cells.

NOTE Confidence: 0.626329596666667

00:23:25.570 --> 00:23:29.254 And we actually confirmed that what

NOTE Confidence: 0.626329596666667

00:23:29.254 --> 00:23:31.710 Justin Balko originally reported

NOTE Confidence: 0.626329596666667

00:23:31.807 --> 00:23:33.994 that the cancers which were positive

NOTE Confidence: 0.626329596666667

00:23:33.994 --> 00:23:36.190 for MHC Class 2 expression actually

NOTE Confidence: 0.626329596666667

00:23:36.252 --> 00:23:38.485 had a higher pathologic CR rate when

NOTE Confidence: 0.626329596666667

00:23:38.485 --> 00:23:40.729 Pembroke was added in the ice spy study.

NOTE Confidence: 0.626329596666667

00:23:40.730 --> 00:23:41.962 But the pathologic CR,

NOTE Confidence: 0.626329596666667

00:23:41.962 --> 00:23:44.124 it was the same whether they were

NOTE Confidence: 0.626329596666667

00:23:44.124 --> 00:23:46.108 MHC Class 2 high or low if they

NOTE Confidence: 0.626329596666667

00:23:46.108 --> 00:23:47.870 only got chemotherapy and so.

NOTE Confidence: 0.626329596666667

00:23:47.870 --> 00:23:49.646 They really strong interaction,

NOTE Confidence: 0.626329596666667

00:23:49.646 --> 00:23:50.978 marker treatment interaction

NOTE Confidence: 0.626329596666667

00:23:50.978 --> 00:23:53.750 in that study and parallel with

NOTE Confidence: 0.626329596666667

00:23:53.750 --> 00:23:55.130 this completely independent.

NOTE Confidence: 0.626329596666667

00:23:55.130 --> 00:23:57.298 Another set of former lab member of mine,

NOTE Confidence: 0.626329596666667

00:23:57.300 --> 00:23:58.716 Jean-paul Bianchini showed the

NOTE Confidence: 0.626329596666667

00:23:58.716 --> 00:24:00.840 same thing in their new adjuvant

NOTE Confidence: 0.626329596666667

00:24:00.901 --> 00:24:02.417 trial without the salesman.

NOTE Confidence: 0.626329596666667

00:24:02.420 --> 00:24:03.036 You know,

NOTE Confidence: 0.626329596666667

00:24:03.036 --> 00:24:04.576 I highlighted for you the

NOTE Confidence: 0.626329596666667

00:24:04.576 --> 00:24:05.500 interaction between Italy,

NOTE Confidence: 0.626329596666667

00:24:05.500 --> 00:24:08.500 the expression on epithelial cells that

NOTE Confidence: 0.626329596666667

00:24:08.500 --> 00:24:11.578 actually predicted higher odds ratio for PCR.

NOTE Confidence: 0.626329596666667

00:24:11.580 --> 00:24:13.561 Vidot is always the map but didn't

NOTE Confidence: 0.626329596666667

00:24:13.561 --> 00:24:15.758 have any sort of significant other

NOTE Confidence: 0.626329596666667

00:24:15.758 --> 00:24:17.474 ratio with chemotherapy alone,

NOTE Confidence: 0.626329596666667

00:24:17.480 --> 00:24:18.419 but the same.

NOTE Confidence: 0.626329596666667

00:24:18.419 --> 00:24:20.610 Study our immune cells didn't carry this.

NOTE Confidence: 0.626329596666667

00:24:20.610 --> 00:24:22.633 So it's a really cool project there

NOTE Confidence: 0.626329596666667

00:24:22.633 --> 00:24:24.954 and we just got funding from the NCI

NOTE Confidence: 0.626329596666667

00:24:24.954 --> 00:24:27.328 to kind of test this and validate this

NOTE Confidence: 0.626329596666667

00:24:27.328 --> 00:24:30.710 in a larger trial them S 1418 that I,

NOTE Confidence: 0.626329596666667

00:24:30.710 --> 00:24:33.010 I mentioned to you earlier.

NOTE Confidence: 0.626329596666667

00:24:33.010 --> 00:24:33.506 But again,

NOTE Confidence: 0.626329596666667

00:24:33.506 --> 00:24:35.242 so this study is the fascinating thing

NOTE Confidence: 0.626329596666667

00:24:35.242 --> 00:24:36.962 about science is that every advance

NOTE Confidence: 0.626329596666667

00:24:36.962 --> 00:24:38.382 actually throws up new questions,

NOTE Confidence: 0.626329596666667

00:24:38.390 --> 00:24:40.574 even more interesting questions.

NOTE Confidence: 0.626329596666667

00:24:40.574 --> 00:24:44.160 So one question is why some cancers

NOTE Confidence: 0.626329596666667

00:24:44.160 --> 00:24:45.659 are important in reach, right?

NOTE Confidence: 0.626329596666667

00:24:45.659 --> 00:24:47.213 A lot of people are struggling

NOTE Confidence: 0.626329596666667

00:24:47.213 --> 00:24:47.990 to find answers,

NOTE Confidence: 0.626329596666667

00:24:47.990 --> 00:24:50.710 how you make a cold against the heart.

NOTE Confidence: 0.626329596666667

00:24:50.710 --> 00:24:52.243 But we thought we ask something a

NOTE Confidence: 0.626329596666667

00:24:52.243 --> 00:24:53.712 little bit more original and maybe

NOTE Confidence: 0.626329596666667

00:24:53.712 --> 00:24:55.810 something that that could be easier to crack.

NOTE Confidence: 0.626329596666667

00:24:55.810 --> 00:24:57.250 And that's the question,

NOTE Confidence: 0.626329596666667

00:24:57.250 --> 00:24:59.050 why doesn't all immune high

NOTE Confidence: 0.626329596666667

00:24:59.050 --> 00:25:01.030 cancers actually accomplished PCR?

NOTE Confidence: 0.626329596666667

00:25:01.030 --> 00:25:02.696 Why is the PCR only 63%?

NOTE Confidence: 0.626329596666667

00:25:02.696 --> 00:25:04.628 And 100 or 90 that's a project

NOTE Confidence: 0.626329596666667

00:25:04.628 --> 00:25:06.651 that Kim actually came women led

NOTE Confidence: 0.626329596666667

00:25:06.651 --> 00:25:08.757 and we compared the immune reach

NOTE Confidence: 0.626329596666667

00:25:08.827 --> 00:25:10.647 triple negative disease that had

NOTE Confidence: 0.626329596666667

00:25:10.647 --> 00:25:13.220 the PCR versus those that did not.

NOTE Confidence: 0.626329596666667

00:25:13.220 --> 00:25:15.470 And we find really pretty interesting

NOTE Confidence: 0.626329596666667

00:25:15.470 --> 00:25:17.496 stuff that I think could lead

NOTE Confidence: 0.626329596666667

00:25:17.496 --> 00:25:19.308 us to some leads about what

NOTE Confidence: 0.853674237272727

00:25:19.382 --> 00:25:20.830 combination therapies,

NOTE Confidence: 0.853674237272727

00:25:20.830 --> 00:25:22.898 immunotherapies could really be

NOTE Confidence: 0.853674237272727

00:25:22.898 --> 00:25:25.483 make embolism and more effective.

NOTE Confidence: 0.853674237272727

00:25:25.490 --> 00:25:27.128 So just to summarize this let's we

NOTE Confidence: 0.853674237272727

00:25:27.128 --> 00:25:28.842 found that the teacher have better if

NOTE Confidence: 0.853674237272727

00:25:28.842 --> 00:25:30.894 one teacher beat is high in the immune

NOTE Confidence: 0.853674237272727

00:25:30.894 --> 00:25:32.868 microenvironment even if you are in reach.

NOTE Confidence: 0.853674237272727

00:25:32.870 --> 00:25:34.772 You don't accomplish PCI and a

NOTE Confidence: 0.853674237272727

00:25:34.772 --> 00:25:36.463 lot of innate immunity markers

NOTE Confidence: 0.853674237272727

00:25:36.463 --> 00:25:38.258 are also associated with it.

NOTE Confidence: 0.853674237272727

00:25:38.260 --> 00:25:40.740 The innate immunity markers actually

NOTE Confidence: 0.853674237272727

00:25:40.740 --> 00:25:43.130 are macrophage and K markers and when

NOTE Confidence: 0.853674237272727

00:25:43.130 --> 00:25:45.597 you look at the cytokine milieu then

NOTE Confidence: 0.853674237272727

00:25:45.597 --> 00:25:47.871 you really see this very strikingly

NOTE Confidence: 0.853674237272727

00:25:47.871 --> 00:25:50.319 so cancers it raises your disease.

NOTE Confidence: 0.853674237272727

00:25:50.320 --> 00:25:52.295 The dominant cytokines are actually

NOTE Confidence: 0.853674237272727

00:25:52.295 --> 00:25:53.875 cytokines which are involved

NOTE Confidence: 0.853674237272727

00:25:53.875 --> 00:25:56.249 in chemotaxis and activation of

NOTE Confidence: 0.853674237272727

00:25:56.249 --> 00:25:57.689 neutrophils and macrophages.

NOTE Confidence: 0.853674237272727

00:25:57.690 --> 00:25:59.210 So we hypothesized they're blocking.

NOTE Confidence: 0.853674237272727

00:25:59.210 --> 00:26:01.190 Some of those would actually improve

NOTE Confidence: 0.853674237272727

00:26:01.190 --> 00:26:05.120 the outcome or the efficacy. Of.

NOTE Confidence: 0.853674237272727

00:26:05.120 --> 00:26:06.784 You actually went pembrolizumab.

NOTE Confidence: 0.853674237272727

00:26:06.784 --> 00:26:09.280 So interestingly I just put that

NOTE Confidence: 0.853674237272727

00:26:09.347 --> 00:26:11.135 asterisk for you to to that.

NOTE Confidence: 0.853674237272727

00:26:11.140 --> 00:26:13.078 It's so beautiful because it congruent.

NOTE Confidence: 0.853674237272727

00:26:13.080 --> 00:26:15.393 So we find that a lot of these very

NOTE Confidence: 0.853674237272727

00:26:15.393 --> 00:26:17.491 same cytokines that we see highly

NOTE Confidence: 0.853674237272727

00:26:17.491 --> 00:26:19.726 present in immune rich non responding

NOTE Confidence: 0.853674237272727

00:26:19.726 --> 00:26:22.120 TNBC at the very same chemokines

NOTE Confidence: 0.853674237272727

00:26:22.120 --> 00:26:24.704 and silicones that we find in the

NOTE Confidence: 0.853674237272727

00:26:24.704 --> 00:26:25.742 microenvironment metastatic disease

NOTE Confidence: 0.853674237272727

00:26:25.742 --> 00:26:28.334 right in that paper that showed that

NOTE Confidence: 0.853674237272727

00:26:28.334 --> 00:26:29.453 the metastatic microenvironment

NOTE Confidence: 0.853674237272727

00:26:29.453 --> 00:26:31.230 is more immuno attenuated.

NOTE Confidence: 0.701418739230769

00:26:33.930 --> 00:26:36.142 Just instead of finish these sort of

NOTE Confidence: 0.701418739230769

00:26:36.142 --> 00:26:38.390 series of questions and immunotherapy off.

NOTE Confidence: 0.701418739230769

00:26:38.390 --> 00:26:40.154 So if immunotherapy works

NOTE Confidence: 0.701418739230769

00:26:40.154 --> 00:26:41.477 beautifully entrepreneur disease,

NOTE Confidence: 0.701418739230769

00:26:41.480 --> 00:26:42.950 could it actually work in a

NOTE Confidence: 0.701418739230769

00:26:42.950 --> 00:26:44.390 subset of ER positive cancers.

NOTE Confidence: 0.701418739230769

00:26:44.390 --> 00:26:47.142 And we think that it will work because

NOTE Confidence: 0.701418739230769

00:26:47.142 --> 00:26:49.760 we noticed in the eye spy trial data

NOTE Confidence: 0.701418739230769

00:26:49.760 --> 00:26:52.073 that in three arms that included

NOTE Confidence: 0.701418739230769

00:26:52.073 --> 00:26:55.079 immunotherapy including the door volume up,

NOTE Confidence: 0.701418739230769

00:26:55.080 --> 00:26:56.520 Olaparib arm, the Iliad,

NOTE Confidence: 0.701418739230769

00:26:56.520 --> 00:26:59.238 the Penrose Metaxa arm and the pembrolizumab

NOTE Confidence: 0.701418739230769

00:26:59.238 --> 00:27:02.160 and it's all like receptor antagonist.

NOTE Confidence: 0.701418739230769

00:27:02.160 --> 00:27:04.610 Arm in all of these three arms

NOTE Confidence: 0.701418739230769

00:27:04.610 --> 00:27:06.707 independently we saw that among the

NOTE Confidence: 0.701418739230769

00:27:06.707 --> 00:27:08.968 ER positive here we call them HR

NOTE Confidence: 0.701418739230769

00:27:09.041 --> 00:27:11.377 hormone receptor positive cancers.

NOTE Confidence: 0.701418739230769

00:27:11.380 --> 00:27:15.076 There is a group that is characterized by

NOTE Confidence: 0.701418739230769

00:27:15.076 --> 00:27:18.078 routinely reported sort of molecular feature,

NOTE Confidence: 0.701418739230769

00:27:18.080 --> 00:27:20.900 the ultra high mammaprint status.

NOTE Confidence: 0.701418739230769

00:27:20.900 --> 00:27:22.226 So all of these patients had

NOTE Confidence: 0.701418739230769

00:27:22.226 --> 00:27:23.460 to have high mammaprint result.

NOTE Confidence: 0.701418739230769

00:27:23.460 --> 00:27:25.112 High MAMMAPRINT defines patient

NOTE Confidence: 0.701418739230769

00:27:25.112 --> 00:27:26.764 superficially benefit from chemotherapy

NOTE Confidence: 0.701418739230769

00:27:26.764 --> 00:27:28.463 but within that high mountain

NOTE Confidence: 0.701418739230769

00:27:28.463 --> 00:27:30.107 group you can devise an agent,

NOTE Confidence: 0.701418739230769

00:27:30.110 --> 00:27:32.200 they actually introduce their system.

NOTE Confidence: 0.701418739230769

00:27:32.200 --> 00:27:33.970 The device to group smaller print

NOTE Confidence: 0.701418739230769

00:27:33.970 --> 00:27:35.949 high high and some Withrow high.

NOTE Confidence: 0.701418739230769

00:27:35.950 --> 00:27:37.546 So the small print we throw higher

NOTE Confidence: 0.701418739230769

00:27:37.546 --> 00:27:39.689 MP two group is the subset among the

NOTE Confidence: 0.701418739230769

00:27:39.689 --> 00:27:41.094 ER positive patients who benefited

NOTE Confidence: 0.701418739230769

00:27:41.152 --> 00:27:42.386 and it's really, really elegant.

NOTE Confidence: 0.701418739230769

00:27:42.386 --> 00:27:43.526 You can't see that right.

NOTE Confidence: 0.701418739230769

00:27:43.530 --> 00:27:45.870 So the HR positive MP1,

NOTE Confidence: 0.701418739230769

00:27:45.870 --> 00:27:47.098 there's no difference whether

NOTE Confidence: 0.701418739230769

00:27:47.098 --> 00:27:48.633 you get chemo plus durva,

NOTE Confidence: 0.701418739230769

00:27:48.640 --> 00:27:50.341 but if you are MP two then

NOTE Confidence: 0.701418739230769

00:27:50.341 --> 00:27:51.330 Nirvana improves your PCR.

NOTE Confidence: 0.701418739230769

00:27:51.330 --> 00:27:52.770 It's same for pembrolizumab

NOTE Confidence: 0.701418739230769

00:27:52.770 --> 00:27:54.570 with the other two arms.

NOTE Confidence: 0.701418739230769

00:27:54.570 --> 00:27:56.130 And what's even nicer when you

NOTE Confidence: 0.701418739230769

00:27:56.130 --> 00:27:57.528 look at the molecular features

NOTE Confidence: 0.701418739230769

00:27:57.528 --> 00:27:59.068 of these empty two patients,

NOTE Confidence: 0.701418739230769

00:27:59.070 --> 00:28:00.810 the area are positive but

NOTE Confidence: 0.701418739230769

00:28:00.810 --> 00:28:02.202 their ER signaling and.

NOTE Confidence: 0.701418739230769

00:28:02.210 --> 00:28:02.540 Yeah,

NOTE Confidence: 0.701418739230769

00:28:02.540 --> 00:28:04.850 sort of the gene signatures that typically

NOTE Confidence: 0.701418739230769

00:28:04.850 --> 00:28:06.699 associated with endocrine sensitivity,

NOTE Confidence: 0.701418739230769

00:28:06.700 --> 00:28:07.321 this is low.

NOTE Confidence: 0.701418739230769

00:28:07.321 --> 00:28:08.563 So that's the group let's see

NOTE Confidence: 0.701418739230769

00:28:08.563 --> 00:28:10.376 are positive but least likely to

NOTE Confidence: 0.701418739230769

00:28:10.376 --> 00:28:11.620 benefit from endocrine treatment.

NOTE Confidence: 0.701418739230769

00:28:11.620 --> 00:28:13.650 They have sort of a higher proliferation

NOTE Confidence: 0.701418739230769

00:28:13.650 --> 00:28:15.139 signature which also makes sense.

NOTE Confidence: 0.701418739230769

00:28:15.140 --> 00:28:17.030 So they are more sensitive to chemotherapy

NOTE Confidence: 0.701418739230769

00:28:17.030 --> 00:28:18.897 and we also saw this in the the,

NOTE Confidence: 0.701418739230769

00:28:18.900 --> 00:28:20.690 the chemotherapy arms and but

NOTE Confidence: 0.701418739230769

00:28:20.690 --> 00:28:22.958 we didn't really see a major

NOTE Confidence: 0.701418739230769

00:28:22.958 --> 00:28:24.988 difference in the immune micro

NOTE Confidence: 0.701418739230769

00:28:24.988 --> 00:28:27.100 in in immune signature genes.

NOTE Confidence: 0.701418739230769

00:28:27.100 --> 00:28:30.594 So again we hope to launch the prospective

NOTE Confidence: 0.701418739230769

00:28:30.594 --> 00:28:32.436 study that would validate this concept.

NOTE Confidence: 0.701418739230769

00:28:32.440 --> 00:28:34.816 With the routinely available essay we

NOTE Confidence: 0.701418739230769

00:28:34.816 --> 00:28:37.113 could actually identify a group that

NOTE Confidence: 0.701418739230769

00:28:37.113 --> 00:28:39.360 will benefit from the same way as

NOTE Confidence: 0.701418739230769

00:28:39.360 --> 00:28:41.887 triple negative disease benefited from

NOTE Confidence: 0.701418739230769

00:28:41.887 --> 00:28:44.027 including immune checkpoint therapy.

NOTE Confidence: 0.701418739230769

00:28:44.030 --> 00:28:45.902 So just to summarize these clinical

NOTE Confidence: 0.701418739230769

00:28:45.902 --> 00:28:47.424 partially the paradigm shift that

NOTE Confidence: 0.701418739230769

00:28:47.424 --> 00:28:48.957 happened in the past sort of 20

NOTE Confidence: 0.701418739230769

00:28:48.957 --> 00:28:50.766 years is that the best way to treat

NOTE Confidence: 0.701418739230769

00:28:50.766 --> 00:28:52.326 most stage two and stage three

NOTE Confidence: 0.701418739230769

00:28:52.326 --> 00:28:54.016 triple negative patients is new

NOTE Confidence: 0.701418739230769

00:28:54.016 --> 00:28:55.609 adjuvant chemotherapy and the best

NOTE Confidence: 0.701418739230769

00:28:55.609 --> 00:28:56.929 PCR rates are accomplished about

NOTE Confidence: 0.701418739230769

00:28:56.929 --> 00:28:59.016 two third of the patients having a

NOTE Confidence: 0.701418739230769

00:28:59.016 --> 00:29:00.566 competent navigation of the cancer,

NOTE Confidence: 0.701418739230769

00:29:00.570 --> 00:29:01.998 the same happened in her two

NOTE Confidence: 0.701418739230769

00:29:01.998 --> 00:29:02.474 positive disease.

NOTE Confidence: 0.701418739230769

00:29:02.480 --> 00:29:04.178 Don't talk about this because it's

NOTE Confidence: 0.701418739230769

00:29:04.178 --> 00:29:06.030 really predated at least by 1015 years,

NOTE Confidence: 0.701418739230769

00:29:06.030 --> 00:29:07.077 the immunotherapy revolution

NOTE Confidence: 0.701418739230769

00:29:07.077 --> 00:29:09.520 and there are a lot of really

NOTE Confidence: 0.701418739230769

00:29:09.581 --> 00:29:11.566 interesting studies that will push

NOTE Confidence: 0.701418739230769

00:29:11.566 --> 00:29:13.551 the survival even further among

NOTE Confidence: 0.701418739230769

00:29:13.614 --> 00:29:15.539 those who have residual disease.

NOTE Confidence: 0.701418739230769

00:29:15.540 --> 00:29:17.328 So there are new studies that

NOTE Confidence: 0.701418739230769

00:29:17.328 --> 00:29:19.201 are launched in that space that

NOTE Confidence: 0.701418739230769

00:29:19.201 --> 00:29:21.037 I kind of highlighted for you.

NOTE Confidence: 0.701418739230769

00:29:21.040 --> 00:29:21.595 So what's next,

NOTE Confidence: 0.701418739230769

00:29:21.595 --> 00:29:21.780 right.

NOTE Confidence: 0.701418739230769

00:29:21.780 --> 00:29:22.890 So what's going to be the

NOTE Confidence: 0.804587020555556

00:29:22.935 --> 00:29:24.519 next paradigm shift in the next 10 years?

NOTE Confidence: 0.804587020555556

00:29:24.520 --> 00:29:27.656 And I think the this is really.

NOTE Confidence: 0.804587020555556

00:29:27.660 --> 00:29:30.215 I I see two really potentially very

NOTE Confidence: 0.804587020555556

00:29:30.215 --> 00:29:32.358 high impact fields which we could

NOTE Confidence: 0.804587020555556

00:29:32.358 --> 00:29:34.118 improve again survival within the

NOTE Confidence: 0.804587020555556

00:29:34.118 --> 00:29:36.116 next 5 to 10 years and which is.

NOTE Confidence: 0.804587020555556

00:29:36.120 --> 00:29:38.460 So wait a second.

NOTE Confidence: 0.803463255714286

00:29:40.990 --> 00:29:43.622 Yeah. So what is coming up with this

NOTE Confidence: 0.803463255714286

00:29:43.622 --> 00:29:45.905 concept that could we detect molecular

NOTE Confidence: 0.803463255714286

00:29:45.905 --> 00:29:49.101 relapse in solid tumors the same way as

NOTE Confidence: 0.803463255714286

00:29:49.101 --> 00:29:51.465 we detect molecular relapse in leukemia.

NOTE Confidence: 0.803463255714286

00:29:51.470 --> 00:29:53.374 So if you see that with PCR that

NOTE Confidence: 0.803463255714286

00:29:53.374 --> 00:29:55.119 your genomic abnormalities returned,

NOTE Confidence: 0.803463255714286

00:29:55.120 --> 00:29:56.428 then a second round of treatment

NOTE Confidence: 0.803463255714286

00:29:56.428 --> 00:29:57.622 at that point would actually

NOTE Confidence: 0.803463255714286

00:29:57.622 --> 00:29:59.017 cure some people from leukemia.

NOTE Confidence: 0.803463255714286

00:29:59.020 --> 00:30:01.127 So could the same paradigm apply to

NOTE Confidence: 0.803463255714286

00:30:01.127 --> 00:30:02.961 to sometimes it didn't really have

NOTE Confidence: 0.803463255714286

00:30:02.961 --> 00:30:05.438 good ways to catch this and we didn't

NOTE Confidence: 0.803463255714286

00:30:05.438 --> 00:30:07.378 really have good effective drugs

NOTE Confidence: 0.803463255714286

00:30:07.378 --> 00:30:09.168 either 5610 years ago to test this,

NOTE Confidence: 0.803463255714286

00:30:09.170 --> 00:30:11.154 but now we have we have most molecular.

NOTE Confidence: 0.803463255714286

00:30:11.160 --> 00:30:13.265 Essays that can pretty reliably

NOTE Confidence: 0.803463255714286

00:30:13.265 --> 00:30:15.917 identify and the SEC DNA is

NOTE Confidence: 0.803463255714286

00:30:15.917 --> 00:30:18.237 particularly tumor informed C DNA.

NOTE Confidence: 0.803463255714286

00:30:18.240 --> 00:30:20.256 So if you have a high C DNA level

NOTE Confidence: 0.803463255714286

00:30:20.256 --> 00:30:22.023 that's starting to rise while you

NOTE Confidence: 0.803463255714286

00:30:22.023 --> 00:30:23.866 are in the surveillance of follow

NOTE Confidence: 0.803463255714286

00:30:23.866 --> 00:30:25.678 up stage of the initial curative

NOTE Confidence: 0.803463255714286

00:30:25.678 --> 00:30:27.604 therapy as the city then rises,

NOTE Confidence: 0.803463255714286

00:30:27.604 --> 00:30:29.970 unfortunately it's almost sure bad that you

NOTE Confidence: 0.803463255714286

00:30:30.035 --> 00:30:32.201 will have a recurrence clinical recurrence

NOTE Confidence: 0.803463255714286

00:30:32.201 --> 00:30:34.609 within the next seven or eight months.

NOTE Confidence: 0.803463255714286

00:30:34.610 --> 00:30:36.640 So could we intervene at that point

NOTE Confidence: 0.803463255714286

00:30:36.640 --> 00:30:38.736 when people are still sort of

NOTE Confidence: 0.803463255714286

00:30:38.736 --> 00:30:40.284 micrometastatic but the micrometastasis

NOTE Confidence: 0.803463255714286

00:30:40.284 --> 00:30:42.080 is raising its ugly head?

NOTE Confidence: 0.803463255714286

00:30:42.080 --> 00:30:43.600 So that's an idea of a second line.

NOTE Confidence: 0.803463255714286

00:30:43.600 --> 00:30:45.340 I look in therapy and we

NOTE Confidence: 0.803463255714286

00:30:45.340 --> 00:30:46.500 actually lead a study.

NOTE Confidence: 0.803463255714286

00:30:46.500 --> 00:30:48.840 We have a study in that space that that's

NOTE Confidence: 0.803463255714286

00:30:48.840 --> 00:30:50.827 exactly this idea in your positive

NOTE Confidence: 0.803463255714286

00:30:50.827 --> 00:30:52.497 patients who are receiving endocrine

NOTE Confidence: 0.803463255714286

00:30:52.558 --> 00:30:54.630 therapy but start to have a rising CDN,

NOTE Confidence: 0.803463255714286

00:30:54.630 --> 00:30:56.154 they randomized the full

NOTE Confidence: 0.803463255714286

00:30:56.154 --> 00:30:57.678 Western public cycling and.

NOTE Confidence: 0.803463255714286

00:30:57.680 --> 00:31:00.312 And we'll just continue with their standard

NOTE Confidence: 0.803463255714286

00:31:00.312 --> 00:31:02.850 of care treatment and get treatment

NOTE Confidence: 0.803463255714286

00:31:02.850 --> 00:31:05.085 when they become clinically symptomatic.

NOTE Confidence: 0.803463255714286

00:31:05.090 --> 00:31:06.585 So the other potentially paradigm

NOTE Confidence: 0.803463255714286

00:31:06.585 --> 00:31:08.458 shifting idea is really that they

NOTE Confidence: 0.803463255714286

00:31:08.458 --> 00:31:10.068 could cure some metastatic disease.

NOTE Confidence: 0.803463255714286

00:31:10.070 --> 00:31:12.070 So you have metastatic disease kind of the

NOTE Confidence: 0.803463255714286

00:31:12.070 --> 00:31:13.910 current dogma is that you will die from it.

NOTE Confidence: 0.803463255714286

00:31:13.910 --> 00:31:15.266 It may take many, many years,

NOTE Confidence: 0.803463255714286

00:31:15.270 --> 00:31:16.522 but ultimately people die.

NOTE Confidence: 0.803463255714286

00:31:16.522 --> 00:31:18.400 I'm not sure that this actually

NOTE Confidence: 0.803463255714286

00:31:18.455 --> 00:31:19.750 has to happen like this.

NOTE Confidence: 0.803463255714286

00:31:19.750 --> 00:31:21.850 So what happened in the past five,

NOTE Confidence: 0.803463255714286

00:31:21.850 --> 00:31:24.022 six years is that you really

NOTE Confidence: 0.803463255714286

00:31:24.022 --> 00:31:25.790 understood much more clearly that

NOTE Confidence: 0.803463255714286

00:31:25.790 --> 00:31:27.830 only that there are multiple.

NOTE Confidence: 0.803463255714286

00:31:27.830 --> 00:31:28.978 Different types of meds,

NOTE Confidence: 0.803463255714286

00:31:28.978 --> 00:31:30.126 not just some medicine.

NOTE Confidence: 0.803463255714286

00:31:30.130 --> 00:31:31.303 Disease doesn't exist.

NOTE Confidence: 0.803463255714286

00:31:31.303 --> 00:31:32.867 There's a homogeneous entity,

NOTE Confidence: 0.803463255714286

00:31:32.870 --> 00:31:34.160 just like the breast cancer doesn't

NOTE Confidence: 0.803463255714286

00:31:34.160 --> 00:31:35.593 exist to looking. It doesn't exist.

NOTE Confidence: 0.803463255714286

00:31:35.593 --> 00:31:36.637 It's a useful concept.

NOTE Confidence: 0.803463255714286

00:31:36.640 --> 00:31:37.680 But practically really these

NOTE Confidence: 0.803463255714286

00:31:37.680 --> 00:31:39.240 are all very there are many,

NOTE Confidence: 0.803463255714286

00:31:39.240 --> 00:31:41.706 many different types of leukemias that

NOTE Confidence: 0.803463255714286

00:31:41.706 --> 00:31:44.050 require different approaches and treatments,

NOTE Confidence: 0.803463255714286

00:31:44.050 --> 00:31:45.250 different types of breast cancers.

NOTE Confidence: 0.803463255714286

00:31:45.250 --> 00:31:47.308 And the same way like metastatic

NOTE Confidence: 0.803463255714286

00:31:47.308 --> 00:31:48.680 disease is also heterogeneous.

NOTE Confidence: 0.803463255714286

00:31:48.680 --> 00:31:51.056 So the novel stage for disease is unique

NOTE Confidence: 0.803463255714286

00:31:51.056 --> 00:31:53.639 because it never received any prior therapy.

NOTE Confidence: 0.803463255714286

00:31:53.640 --> 00:31:55.032 That's obviously very different

NOTE Confidence: 0.803463255714286

00:31:55.032 --> 00:31:56.424 from somebody relapsing and

NOTE Confidence: 0.803463255714286

00:31:56.424 --> 00:31:58.150 having a metastatic disease.

NOTE Confidence: 0.803463255714286

00:31:58.150 --> 00:31:59.404 After they went through all the

NOTE Confidence: 0.803463255714286

00:31:59.404 --> 00:32:00.482 treatments that I showed you

NOTE Confidence: 0.803463255714286

00:32:00.482 --> 00:32:01.477 in the new adjuvant setting,

NOTE Confidence: 0.803463255714286

00:32:01.480 --> 00:32:04.396 the chemotherapies was embolism and whatnot.

NOTE Confidence: 0.803463255714286

00:32:04.400 --> 00:32:05.965 So curing those folks with

NOTE Confidence: 0.803463255714286

00:32:05.965 --> 00:32:07.880 existing therapies is a long shot,

NOTE Confidence: 0.803463255714286

00:32:07.880 --> 00:32:09.518 but curing those folks who never had

NOTE Confidence: 0.803463255714286

00:32:09.518 --> 00:32:10.961 any therapy with the combination of

NOTE Confidence: 0.803463255714286

00:32:10.961 --> 00:32:12.840 drugs is probably not such a long shot.

NOTE Confidence: 0.803463255714286

00:32:12.840 --> 00:32:15.038 And there are many case reports and

NOTE Confidence: 0.803463255714286

00:32:15.038 --> 00:32:16.877 oncologists who practice for a long time.

NOTE Confidence: 0.803463255714286

00:32:16.880 --> 00:32:18.835 All have anecdotal cases of

NOTE Confidence: 0.803463255714286

00:32:18.835 --> 00:32:19.617 metastatic patients,

NOTE Confidence: 0.774022176190476

00:32:19.620 --> 00:32:21.125 particularly with her two positive

NOTE Confidence: 0.774022176190476

00:32:21.125 --> 00:32:22.630 disease because her two positive

NOTE Confidence: 0.774022176190476

00:32:22.680 --> 00:32:24.216 disease had the best drugs initially

NOTE Confidence: 0.774022176190476

00:32:24.216 --> 00:32:25.560 the her two targeted drugs,

NOTE Confidence: 0.774022176190476

00:32:25.560 --> 00:32:27.457 but now we have good drugs for

NOTE Confidence: 0.774022176190476

00:32:27.457 --> 00:32:28.760 for triplet disease as well.

NOTE Confidence: 0.774022176190476

00:32:28.760 --> 00:32:31.178 And also for your poster disease,

NOTE Confidence: 0.774022176190476

00:32:31.180 --> 00:32:32.460 so this paradigm that really

NOTE Confidence: 0.774022176190476

00:32:32.460 --> 00:32:34.758 kind of put into the mind of many

NOTE Confidence: 0.774022176190476

00:32:34.758 --> 00:32:36.353 practicing physicians that some her

NOTE Confidence: 0.774022176190476

00:32:36.353 --> 00:32:38.100 two positive cancer can be cured.

NOTE Confidence: 0.774022176190476

00:32:38.100 --> 00:32:40.206 I think it's kind of increasingly

NOTE Confidence: 0.774022176190476

00:32:40.206 --> 00:32:42.720 applicable to the other subtypes as well.

NOTE Confidence: 0.774022176190476

00:32:42.720 --> 00:32:45.348 So we hope to do a study that would

NOTE Confidence: 0.774022176190476

00:32:45.348 --> 00:32:47.312 actually focus on covad especial

NOTE Confidence: 0.774022176190476

00:32:47.312 --> 00:32:49.706 group of her of metastatic patients,

NOTE Confidence: 0.774022176190476

00:32:49.710 --> 00:32:51.545 they de Novo newly diagnosed

NOTE Confidence: 0.774022176190476

00:32:51.545 --> 00:32:52.646 metastatic patients particularly

NOTE Confidence: 0.774022176190476

00:32:52.646 --> 00:32:54.399 with oligo metastatic disease,

NOTE Confidence: 0.774022176190476

00:32:54.400 --> 00:32:56.659 so that we could really get rid of all

NOTE Confidence: 0.774022176190476

00:32:56.659 --> 00:32:58.889 the known homicides and what's left.

NOTE Confidence: 0.774022176190476

00:32:58.890 --> 00:32:59.444 Is micromass,

NOTE Confidence: 0.774022176190476

00:32:59.444 --> 00:33:01.383 but we can deal with micro Mets.

NOTE Confidence: 0.774022176190476

00:33:01.390 --> 00:33:03.086 That's the success story that I showed you.

NOTE Confidence: 0.774022176190476

00:33:03.090 --> 00:33:04.780 That's how adjuvant therapy improves

NOTE Confidence: 0.774022176190476

00:33:04.780 --> 00:33:06.818 survival after removing the the primary

NOTE Confidence: 0.774022176190476

00:33:06.818 --> 00:33:08.564 breast cancer in the lymph nodes,

NOTE Confidence: 0.774022176190476

00:33:08.570 --> 00:33:09.752 the systemic therapy.

NOTE Confidence: 0.774022176190476

00:33:09.752 --> 00:33:12.116 Washes and and and kills them

NOTE Confidence: 0.774022176190476

00:33:12.116 --> 00:33:13.540 at the Micromax.

NOTE Confidence: 0.774022176190476

00:33:13.540 --> 00:33:15.129 So I think this better than probably

NOTE Confidence: 0.774022176190476

00:33:15.129 --> 00:33:16.828 will hold up in stage four disease

NOTE Confidence: 0.774022176190476

00:33:16.828 --> 00:33:18.274 and the vision is very simple.

NOTE Confidence: 0.774022176190476

00:33:18.280 --> 00:33:20.305 So in in five or ten years you don't

NOTE Confidence: 0.774022176190476

00:33:20.305 --> 00:33:22.507 call these patients the oligo metastatic

NOTE Confidence: 0.774022176190476

00:33:22.510 --> 00:33:23.900 stage four patients stage four,

NOTE Confidence: 0.774022176190476

00:33:23.900 --> 00:33:26.228 but you call them stage 3C.

NOTE Confidence: 0.774022176190476

00:33:26.230 --> 00:33:28.150 Because they are deep, sorry.

NOTE Confidence: 0.774022176190476

00:33:28.150 --> 00:33:30.880 Because then they will be curable.

NOTE Confidence: 0.774022176190476

00:33:30.880 --> 00:33:33.085 So I'm going to move on to some other

NOTE Confidence: 0.774022176190476

00:33:33.085 --> 00:33:35.149 projects that I also find amazing and I

NOTE Confidence: 0.774022176190476

00:33:35.149 --> 00:33:37.237 just wanna share you some of the results.

NOTE Confidence: 0.774022176190476

00:33:37.240 --> 00:33:39.382 So why do some women develop breast

NOTE Confidence: 0.774022176190476

00:33:39.382 --> 00:33:41.218 cancer 20-30 years earlier than the

NOTE Confidence: 0.774022176190476

00:33:41.218 --> 00:33:43.206 average or median age even in the

NOTE Confidence: 0.774022176190476

00:33:43.264 --> 00:33:45.139 absence of any germline mutation?

NOTE Confidence: 0.774022176190476

00:33:45.140 --> 00:33:46.810 Actually that's the majority of

NOTE Confidence: 0.774022176190476

00:33:46.810 --> 00:33:48.480 young women with breast cancer.

NOTE Confidence: 0.774022176190476

00:33:48.480 --> 00:33:50.524 It's only a minority who has broken

NOTE Confidence: 0.774022176190476

00:33:50.524 --> 00:33:51.920 mutations rather identified mutations.

NOTE Confidence: 0.774022176190476

00:33:51.920 --> 00:33:53.380 So we had two ideas.

NOTE Confidence: 0.774022176190476

00:33:53.380 --> 00:33:55.940 One was that each is the strongest non

NOTE Confidence: 0.774022176190476

00:33:55.940 --> 00:33:58.217 genetic risk factor for breast cancer.

NOTE Confidence: 0.774022176190476

00:33:58.220 --> 00:34:00.314 So could you actually sort of

NOTE Confidence: 0.774022176190476

00:34:00.314 --> 00:34:01.710 hypothesize that young women?

NOTE Confidence: 0.774022176190476

00:34:01.710 --> 00:34:04.015 Could be breast cancer actually

NOTE Confidence: 0.774022176190476

00:34:04.015 --> 00:34:05.859 experience an accelerated epigenetic

NOTE Confidence: 0.774022176190476

00:34:05.859 --> 00:34:07.419 age of their breast.

NOTE Confidence: 0.774022176190476

00:34:07.420 --> 00:34:09.396 So this was an idea that Erin Hofstatter,

NOTE Confidence: 0.774022176190476

00:34:09.400 --> 00:34:10.846 our former colleague picked up and

NOTE Confidence: 0.774022176190476

00:34:10.846 --> 00:34:12.531 we did a series of publications

NOTE Confidence: 0.774022176190476

00:34:12.531 --> 00:34:14.196 that actually suggests that this

NOTE Confidence: 0.774022176190476

00:34:14.196 --> 00:34:15.195 is indeed happening.

NOTE Confidence: 0.774022176190476

00:34:15.200 --> 00:34:17.468 So it shows you this insert from

NOTE Confidence: 0.774022176190476

00:34:17.468 --> 00:34:19.209 the the clinical epigenetics paper

NOTE Confidence: 0.774022176190476

00:34:19.209 --> 00:34:21.659 in 2018 shows this the most sort

NOTE Confidence: 0.774022176190476

00:34:21.659 --> 00:34:23.340 of simply and clearly.

NOTE Confidence: 0.774022176190476

00:34:23.340 --> 00:34:25.461 So what you should what you see

NOTE Confidence: 0.774022176190476

00:34:25.461 --> 00:34:27.594 there is each acceleration in the

NOTE Confidence: 0.774022176190476

00:34:27.594 --> 00:34:29.898 normal breast tissue of women who

NOTE Confidence: 0.774022176190476

00:34:29.898 --> 00:34:32.237 had breast cancer later and the.

NOTE Confidence: 0.774022176190476

00:34:32.240 --> 00:34:33.605 Epigenetic age acceleration of people

NOTE Confidence: 0.774022176190476

00:34:33.605 --> 00:34:34.970 who never develop breast cancer.

NOTE Confidence: 0.774022176190476

00:34:34.970 --> 00:34:37.282 So we did this with the Susan Comment

NOTE Confidence: 0.774022176190476

00:34:37.282 --> 00:34:39.805 Tissue Bank and with some tissues from here.

NOTE Confidence: 0.774022176190476

00:34:39.810 --> 00:34:42.330 So you see that there is a

NOTE Confidence: 0.774022176190476

00:34:42.330 --> 00:34:43.050 significant acceleration.

NOTE Confidence: 0.774022176190476

00:34:43.050 --> 00:34:44.942 So epigenetically speaking based

NOTE Confidence: 0.774022176190476

00:34:44.942 --> 00:34:46.834 on the methylation signature,

NOTE Confidence: 0.774022176190476

00:34:46.840 --> 00:34:49.162 the breast normal breast tissues of

NOTE Confidence: 0.774022176190476

00:34:49.162 --> 00:34:51.139 woman who subsequently developed breast

NOTE Confidence: 0.774022176190476

00:34:51.139 --> 00:34:53.729 cancer is older than their chronological age.

NOTE Confidence: 0.774022176190476

00:34:53.730 --> 00:34:55.641 And we don't see this to such

NOTE Confidence: 0.774022176190476

00:34:55.641 --> 00:34:57.609 extent in the control patients.

NOTE Confidence: 0.774022176190476

00:34:57.610 --> 00:34:59.370 And then and then we had some follow

NOTE Confidence: 0.774022176190476

00:34:59.370 --> 00:35:00.958 up patients which really kind of

NOTE Confidence: 0.774022176190476

00:35:00.958 --> 00:35:02.608 papers that explained that it's mostly.

NOTE Confidence: 0.663768066666667

00:35:02.610 --> 00:35:04.438 Polycom related genes whose

NOTE Confidence: 0.663768066666667

00:35:04.438 --> 00:35:06.266 methylation pattern is associated

NOTE Confidence: 0.663768066666667

00:35:06.266 --> 00:35:08.340 with this age acceleration,

NOTE Confidence: 0.663768066666667

00:35:08.340 --> 00:35:10.940 and this last paper on the review in

NOTE Confidence: 0.663768066666667

00:35:10.940 --> 00:35:13.183 science advances shows that actually every

NOTE Confidence: 0.663768066666667

00:35:13.183 --> 00:35:15.845 cell proliferation adds a little bit of

NOTE Confidence: 0.663768066666667

00:35:15.845 --> 00:35:18.050 epigenetic aging to to to the tissues.

NOTE Confidence: 0.663768066666667

00:35:18.050 --> 00:35:20.808 And there is a share of epigenetic

NOTE Confidence: 0.663768066666667

00:35:20.808 --> 00:35:23.001 signature between cancers and and normal

NOTE Confidence: 0.663768066666667

00:35:23.001 --> 00:35:25.710 cells and it relates to aging and it

NOTE Confidence: 0.663768066666667

00:35:25.710 --> 00:35:27.895 relates to ultimately cell divisions.

NOTE Confidence: 0.663768066666667

00:35:27.900 --> 00:35:30.516 But it's probably not the full story though.

NOTE Confidence: 0.663768066666667

00:35:30.520 --> 00:35:32.340 So what's the rest of the story?

NOTE Confidence: 0.663768066666667

00:35:32.340 --> 00:35:34.293 So family history is a predictive risk

NOTE Confidence: 0.663768066666667

00:35:34.293 --> 00:35:36.614 factor even in the absence of any

NOTE Confidence: 0.663768066666667

00:35:36.614 --> 00:35:38.399 detectable hyper reference gene mutations,

NOTE Confidence: 0.663768066666667

00:35:38.400 --> 00:35:40.125 right? So something you inherited

NOTE Confidence: 0.663768066666667

00:35:40.125 --> 00:35:41.160 increases your risk,

NOTE Confidence: 0.663768066666667

00:35:41.160 --> 00:35:44.200 even if it's you can't see it so.

NOTE Confidence: 0.663768066666667

00:35:44.200 --> 00:35:46.960 Polygenic risk scores that use individual

NOTE Confidence: 0.663768066666667

00:35:46.960 --> 00:35:49.233 snips that are individually associated

NOTE Confidence: 0.663768066666667

00:35:49.233 --> 00:35:51.795 with risk to a very small extent,

NOTE Confidence: 0.663768066666667

00:35:51.800 --> 00:35:53.284 sum them up and you've made them

NOTE Confidence: 0.663768066666667

00:35:53.284 --> 00:35:54.799 by the risk that they confer.

NOTE Confidence: 0.663768066666667

00:35:54.800 --> 00:35:55.960 That's a polygenic risk score.

NOTE Confidence: 0.663768066666667

00:35:55.960 --> 00:35:56.342 However,

NOTE Confidence: 0.663768066666667

00:35:56.342 --> 00:35:59.016 even the best ones today using several

NOTE Confidence: 0.663768066666667

00:35:59.016 --> 00:36:00.932 100 risks polygenic risk and have

NOTE Confidence: 0.663768066666667

00:36:00.932 --> 00:36:03.000 a lot of missing heredity in them.

NOTE Confidence: 0.663768066666667

00:36:03.000 --> 00:36:05.296 So they don't explain this complete story.

NOTE Confidence: 0.663768066666667

00:36:05.300 --> 00:36:07.524 So we have this other idea that could

NOTE Confidence: 0.663768066666667

00:36:07.524 --> 00:36:09.504 the combination of non recurrent rare

NOTE Confidence: 0.663768066666667

00:36:09.504 --> 00:36:11.209 germline variants and cancer relevant

NOTE Confidence: 0.663768066666667

00:36:11.209 --> 00:36:13.029 genes determined individual risk.

NOTE Confidence: 0.663768066666667

00:36:13.030 --> 00:36:14.326 So because they are not recurrent.

NOTE Confidence: 0.663768066666667

00:36:14.330 --> 00:36:16.286 Missed them in in indigenous studies,

NOTE Confidence: 0.663768066666667

00:36:16.290 --> 00:36:16.621 right,

NOTE Confidence: 0.663768066666667

00:36:16.621 --> 00:36:18.607 because they start out finding individual

NOTE Confidence: 0.663768066666667

00:36:18.607 --> 00:36:20.292 snips that are associated because

NOTE Confidence: 0.663768066666667

00:36:20.292 --> 00:36:22.188 they are recurrent in the mental

NOTE Confidence: 0.663768066666667

00:36:22.188 --> 00:36:23.810 state of India's cancer population.

NOTE Confidence: 0.663768066666667

00:36:23.810 --> 00:36:25.460 But if it's not recurrent,

NOTE Confidence: 0.663768066666667

00:36:25.460 --> 00:36:27.760 you won't see it.

NOTE Confidence: 0.663768066666667

00:36:27.760 --> 00:36:29.767 So this is an idea that really kind of

NOTE Confidence: 0.663768066666667

00:36:29.767 --> 00:36:31.637 wanted me for quite a while since this

NOTE Confidence: 0.663768066666667

00:36:31.637 --> 00:36:33.807 paper came out from the 1000 Genome Project,

NOTE Confidence: 0.663768066666667

00:36:33.810 --> 00:36:35.316 which showed that all of us

NOTE Confidence: 0.663768066666667

00:36:35.316 --> 00:36:36.320 here have different faces.

NOTE Confidence: 0.663768066666667

00:36:36.320 --> 00:36:38.714 And the reason we have different faces

NOTE Confidence: 0.663768066666667

00:36:38.714 --> 00:36:41.185 is this amazing set of variation in

NOTE Confidence: 0.663768066666667

00:36:41.185 --> 00:36:43.870 Snips and Jermaine Snips and other

NOTE Confidence: 0.663768066666667

00:36:43.870 --> 00:36:47.720 genomic variations that we are born with.

NOTE Confidence: 0.663768066666667

00:36:47.720 --> 00:36:50.456 So an average person carries about

NOTE Confidence: 0.663768066666667

00:36:50.456 --> 00:36:53.648 20 and 50 to 350 genes that have

NOTE Confidence: 0.663768066666667

00:36:53.648 --> 00:36:55.016 a loss of function.

NOTE Confidence: 0.663768066666667

00:36:55.020 --> 00:36:56.490 That's probably the reason why I have

NOTE Confidence: 0.663768066666667

00:36:56.490 --> 00:36:57.879 this poor voice and small stature.

NOTE Confidence: 0.663768066666667

00:36:57.880 --> 00:36:58.582 But anyway,

NOTE Confidence: 0.663768066666667

00:36:58.582 --> 00:37:01.039 so the point is that this low

NOTE Confidence: 0.663768066666667

00:37:01.039 --> 00:37:03.707 frequency events that occur in unique

NOTE Confidence: 0.663768066666667

00:37:03.707 --> 00:37:05.947 combination individuals might set the

NOTE Confidence: 0.663768066666667

00:37:06.020 --> 00:37:08.400 stage that what additional events

NOTE Confidence: 0.663768066666667

00:37:08.400 --> 00:37:10.780 matter or cause the transformation.

NOTE Confidence: 0.663768066666667

00:37:10.780 --> 00:37:14.285 So it's a combinatorial effect, right?

NOTE Confidence: 0.663768066666667

00:37:14.285 --> 00:37:15.890 So.

NOTE Confidence: 0.663768066666667

00:37:15.890 --> 00:37:17.995 We put these hypothesis forward

NOTE Confidence: 0.663768066666667

00:37:17.995 --> 00:37:20.100 that really that functional germline

NOTE Confidence: 0.663768066666667

00:37:20.169 --> 00:37:22.339 variants as potential Co oncogenes.

NOTE Confidence: 0.663768066666667

00:37:22.340 --> 00:37:24.632 And this actually I think there's

NOTE Confidence: 0.663768066666667

00:37:24.632 --> 00:37:26.960 something that covers on the screen.

NOTE Confidence: 0.663768066666667

00:37:26.960 --> 00:37:28.675 Yeah, so you can't see this well,

NOTE Confidence: 0.663768066666667

00:37:28.680 --> 00:37:29.505 but this model,

NOTE Confidence: 0.663768066666667

00:37:29.505 --> 00:37:31.430 the the nice thing about models is

NOTE Confidence: 0.663768066666667

00:37:31.485 --> 00:37:33.649 they predict testable hypothesis, right.

NOTE Confidence: 0.663768066666667

00:37:33.649 --> 00:37:35.743 So this particular idea that the

NOTE Confidence: 0.663768066666667

00:37:35.743 --> 00:37:37.432 Germans polymorphisms all of them

NOTE Confidence: 0.663768066666667

00:37:37.432 --> 00:37:39.172 together said this theme stage for

NOTE Confidence: 0.663768066666667

00:37:39.172 --> 00:37:41.342 what counts as an oncogenic event and

NOTE Confidence: 0.663768066666667

00:37:41.342 --> 00:37:43.296 eventually this is the totality of

NOTE Confidence: 0.663768066666667

00:37:43.296 --> 00:37:45.376 abnormalities that lead to cancer.

NOTE Confidence: 0.663768066666667

00:37:45.380 --> 00:37:48.173 So it's this sort of testable leads

NOTE Confidence: 0.663768066666667

00:37:48.173 --> 00:37:50.300 to this testable hypothesis,

NOTE Confidence: 0.663768066666667

00:37:50.300 --> 00:37:52.448 right that cancers in younger patients.

NOTE Confidence: 0.663768066666667

00:37:52.450 --> 00:37:53.440 This is correct.

NOTE Confidence: 0.663768066666667

00:37:53.440 --> 00:37:55.420 They should have more germline variants

NOTE Confidence: 0.663768066666667

00:37:55.420 --> 00:37:57.003 because they need fewer somatic

NOTE Confidence: 0.663768066666667

00:37:57.003 --> 00:37:58.951 events to reach a threshold, right?

NOTE Confidence: 0.663768066666667

00:37:58.951 --> 00:38:00.755 The sexual disturbance that

NOTE Confidence: 0.663768066666667

00:38:00.755 --> 00:38:03.010 pushed them over to to

NOTE Confidence: 0.720834559166667

00:38:03.094 --> 00:38:04.440 become malignant.

NOTE Confidence: 0.720834559166667

00:38:04.440 --> 00:38:06.150 And theoretically you could also

NOTE Confidence: 0.720834559166667

00:38:06.150 --> 00:38:08.635 use this idea to develop a cancer

NOTE Confidence: 0.720834559166667

00:38:08.635 --> 00:38:10.405 gene systems integrity score that

NOTE Confidence: 0.720834559166667

00:38:10.405 --> 00:38:13.369 captures how far a cell or tissue is

NOTE Confidence: 0.720834559166667

00:38:13.369 --> 00:38:14.837 from this malignant transformation.

NOTE Confidence: 0.720834559166667

00:38:14.840 --> 00:38:17.210 So we started to study that.

NOTE Confidence: 0.720834559166667

00:38:17.210 --> 00:38:19.352 And this is a paper that

NOTE Confidence: 0.720834559166667

00:38:19.352 --> 00:38:21.469 touching postdoc in my lab did.

NOTE Confidence: 0.720834559166667

00:38:21.470 --> 00:38:23.534 So we asked this really fundamental

NOTE Confidence: 0.720834559166667

00:38:23.534 --> 00:38:25.568 simple thing that amazingly not a

NOTE Confidence: 0.720834559166667

00:38:25.568 --> 00:38:27.368 lot of people actually studied before

NOTE Confidence: 0.720834559166667

00:38:27.368 --> 00:38:29.175 that what's the relationship between

NOTE Confidence: 0.720834559166667

00:38:29.175 --> 00:38:32.276 the person's age of that each of your

NOTE Confidence: 0.720834559166667

00:38:32.276 --> 00:38:34.862 diagnosis of cancer and the germline

NOTE Confidence: 0.720834559166667

00:38:34.862 --> 00:38:37.550 variant load in cancer relevant genes.

NOTE Confidence: 0.720834559166667

00:38:37.550 --> 00:38:39.050 So what are cancer relevant genes?

NOTE Confidence: 0.720834559166667

00:38:39.050 --> 00:38:41.143 So we just put from the literature

NOTE Confidence: 0.720834559166667

00:38:41.143 --> 00:38:43.410 and from from review articles about

NOTE Confidence: 0.720834559166667

00:38:43.410 --> 00:38:45.685 1500 genes which are experimentally

NOTE Confidence: 0.720834559166667

00:38:45.685 --> 00:38:47.505 validated that they alter.

NOTE Confidence: 0.720834559166667

00:38:47.510 --> 00:38:48.854 They've played an important

NOTE Confidence: 0.720834559166667

00:38:48.854 --> 00:38:50.198 biological role in cancer.

NOTE Confidence: 0.720834559166667

00:38:50.200 --> 00:38:51.320 And when you see here,

NOTE Confidence: 0.720834559166667

00:38:51.320 --> 00:38:52.930 it's actually pretty obvious and

NOTE Confidence: 0.720834559166667

00:38:52.930 --> 00:38:54.305 it's really beautiful, right.

NOTE Confidence: 0.720834559166667

00:38:54.305 --> 00:38:56.735 So people who develop cancer at

NOTE Confidence: 0.720834559166667

00:38:56.735 --> 00:38:59.540 an older age have fewer germline

NOTE Confidence: 0.720834559166667

00:38:59.540 --> 00:39:01.898 alterations in these cancer relevant genes.

NOTE Confidence: 0.720834559166667

00:39:01.900 --> 00:39:03.110 People who develop cancer at

NOTE Confidence: 0.720834559166667

00:39:03.110 --> 00:39:04.700 younger age have a much higher,

NOTE Confidence: 0.720834559166667

00:39:04.700 --> 00:39:07.902 these are age bins by years of 10 and the

NOTE Confidence: 0.720834559166667

00:39:07.902 --> 00:39:10.079 opposite is seen in the somatic space.

NOTE Confidence: 0.720834559166667

00:39:10.080 --> 00:39:11.760 So people will develop cancer at their ages.

NOTE Confidence: 0.720834559166667

00:39:11.760 --> 00:39:12.675 Prostate cancer folks

NOTE Confidence: 0.720834559166667

00:39:12.675 --> 00:39:14.200 have a lot of mutations,

NOTE Confidence: 0.720834559166667

00:39:14.200 --> 00:39:15.495 whereas people who develop cancer

NOTE Confidence: 0.720834559166667

00:39:15.495 --> 00:39:17.520 at an early age have fewer somatic.

NOTE Confidence: 0.720834559166667

00:39:17.520 --> 00:39:17.809 Positions,

NOTE Confidence: 0.720834559166667

00:39:17.809 --> 00:39:19.543 and we knew this from the

NOTE Confidence: 0.720834559166667

00:39:19.543 --> 00:39:20.410 pediatric literature actually.

NOTE Confidence: 0.720834559166667

00:39:20.410 --> 00:39:21.502 Pediatric cancers don't have

NOTE Confidence: 0.720834559166667

00:39:21.502 --> 00:39:23.790 a heck of a lot of mutations.

NOTE Confidence: 0.720834559166667

00:39:23.790 --> 00:39:25.589 So that's actually a really nice story

NOTE Confidence: 0.720834559166667

00:39:25.589 --> 00:39:27.257 that that supports this idea that

NOTE Confidence: 0.720834559166667

00:39:27.257 --> 00:39:28.667 somehow that's the combined effect.

NOTE Confidence: 0.720834559166667

00:39:28.670 --> 00:39:30.254 And if you have a lot of germline hits,

NOTE Confidence: 0.720834559166667

00:39:30.260 --> 00:39:33.098 you need need a fewer random

NOTE Confidence: 0.720834559166667

00:39:33.098 --> 00:39:35.959 somatic hits to push you over.

NOTE Confidence: 0.720834559166667

00:39:35.960 --> 00:39:36.908 In this paper view,

NOTE Confidence: 0.720834559166667

00:39:36.908 --> 00:39:38.643 it kind of did you think a

NOTE Confidence: 0.720834559166667

00:39:38.643 --> 00:39:40.167 little bit deeper and you know,

NOTE Confidence: 0.720834559166667

00:39:40.170 --> 00:39:42.750 so cancers which actually are highly

NOTE Confidence: 0.720834559166667

00:39:42.750 --> 00:39:44.690 linked to environmental factors for

NOTE Confidence: 0.720834559166667

00:39:44.690 --> 00:39:46.850 lung cancer for example that they

NOTE Confidence: 0.720834559166667

00:39:46.850 --> 00:39:48.765 actually tend to have a lot more

NOTE Confidence: 0.720834559166667

00:39:48.765 --> 00:39:50.190 somatic events and some somatic

NOTE Confidence: 0.720834559166667

00:39:50.190 --> 00:39:51.462 mutations from somatic origin,

NOTE Confidence: 0.720834559166667

00:39:51.462 --> 00:39:53.052 from germline in other cancers

NOTE Confidence: 0.720834559166667

00:39:53.052 --> 00:39:53.909 kind of coffee.

NOTE Confidence: 0.720834559166667

00:39:53.910 --> 00:39:55.958 So in between and some of them are

NOTE Confidence: 0.720834559166667

00:39:55.958 --> 00:39:57.429 actually like testicular germs,

NOTE Confidence: 0.720834559166667

00:39:57.430 --> 00:39:59.755 atoms are dominated by germline

NOTE Confidence: 0.720834559166667

00:39:59.755 --> 00:40:02.080 hits rather than somatic hits.

NOTE Confidence: 0.7001029925

00:40:04.550 --> 00:40:07.189 But then this this location OK so

NOTE Confidence: 0.7001029925

00:40:07.189 --> 00:40:09.345 why 1500 genes so probably are

NOTE Confidence: 0.7001029925

00:40:09.345 --> 00:40:11.650 there more genes related to cancer.

NOTE Confidence: 0.7001029925

00:40:11.650 --> 00:40:14.219 So we we asked this question whether

NOTE Confidence: 0.7001029925

00:40:14.219 --> 00:40:16.157 what's the what's the totality

NOTE Confidence: 0.7001029925

00:40:16.157 --> 00:40:18.062 of cancer relevant human genes

NOTE Confidence: 0.7001029925

00:40:18.062 --> 00:40:20.976 and the name we came up with the

NOTE Confidence: 0.7001029925

00:40:20.976 --> 00:40:22.676 really simple concept that if.

NOTE Confidence: 0.7001029925

00:40:22.680 --> 00:40:24.235 Core cancer genes are important

NOTE Confidence: 0.7001029925

00:40:24.235 --> 00:40:26.185 and we define core cancer genes

NOTE Confidence: 0.7001029925

00:40:26.185 --> 00:40:27.865 actually from a clinical panel,

NOTE Confidence: 0.7001029925

00:40:27.870 --> 00:40:30.192 the MSKCC impact panel that's clinically

NOTE Confidence: 0.7001029925

00:40:30.192 --> 00:40:32.620 used to define actual permutations.

NOTE Confidence: 0.7001029925

00:40:32.620 --> 00:40:35.052 So these hypothesized the

NOTE Confidence: 0.7001029925

00:40:35.052 --> 00:40:38.092 genes that interact in a.

NOTE Confidence: 0.7001029925

00:40:38.100 --> 00:40:39.785 Putting putting interaction network or

NOTE Confidence: 0.7001029925

00:40:39.785 --> 00:40:42.392 the string network that there's a lot of

NOTE Confidence: 0.7001029925

00:40:42.392 --> 00:40:43.837 different ways to measure interactions.

NOTE Confidence: 0.7001029925

00:40:43.840 --> 00:40:45.422 So genes that interact with the core

NOTE Confidence: 0.7001029925

00:40:45.422 --> 00:40:46.977 genes will be somewhat important and

NOTE Confidence: 0.7001029925

00:40:46.977 --> 00:40:48.909 genes that interact with this one step

NOTE Confidence: 0.7001029925

00:40:48.955 --> 00:40:50.419 remove genes will also be important

NOTE Confidence: 0.7001029925

00:40:50.419 --> 00:40:51.996 to some extent but probably less.

NOTE Confidence: 0.7001029925

00:40:51.996 --> 00:40:54.082 And then those which are three four

NOTE Confidence: 0.7001029925

00:40:54.082 --> 00:40:56.136 steps removed are even less important.

NOTE Confidence: 0.7001029925

00:40:56.140 --> 00:40:58.079 So we wanted to test this hypothesis,

NOTE Confidence: 0.7001029925

00:40:58.080 --> 00:41:00.168 but as you get closer to the close genes

NOTE Confidence: 0.7001029925

00:41:00.168 --> 00:41:02.476 then you would have increasing connectivity.

NOTE Confidence: 0.7001029925

00:41:02.480 --> 00:41:04.892 That's one mathematical way to measure

NOTE Confidence: 0.7001029925

00:41:04.892 --> 00:41:07.760 the importance of gene as you get closer.

NOTE Confidence: 0.7001029925

00:41:07.760 --> 00:41:08.513 So one step.

NOTE Confidence: 0.7001029925

00:41:08.513 --> 00:41:10.019 Both from from core cancer genes

NOTE Confidence: 0.7001029925

00:41:10.019 --> 00:41:12.245 then it's going to be more important

NOTE Confidence: 0.7001029925

00:41:12.245 --> 00:41:12.885 than survivability.

NOTE Confidence: 0.7001029925

00:41:12.890 --> 00:41:14.996 We can check this in genome

NOTE Confidence: 0.7001029925

00:41:14.996 --> 00:41:17.030 wide CRISPR and ASARONE screens.

NOTE Confidence: 0.7001029925

00:41:17.030 --> 00:41:18.465 Also predicted genes which are

NOTE Confidence: 0.7001029925

00:41:18.465 --> 00:41:19.326 one step removed,

NOTE Confidence: 0.7001029925

00:41:19.330 --> 00:41:21.451 2 steps removed are more important than

NOTE Confidence: 0.7001029925

00:41:21.451 --> 00:41:23.306 those which are three steps removed

NOTE Confidence: 0.7001029925

00:41:23.306 --> 00:41:25.385 in terms of having large number of

NOTE Confidence: 0.7001029925

00:41:25.445 --> 00:41:27.161 somatic mutations in in Kansas and

NOTE Confidence: 0.7001029925

00:41:27.161 --> 00:41:29.420 that they will be under a stronger

NOTE Confidence: 0.7001029925

00:41:29.420 --> 00:41:31.270 negative selection in the germline,

NOTE Confidence: 0.7001029925

00:41:31.270 --> 00:41:31.590 right,

NOTE Confidence: 0.7001029925

00:41:31.590 --> 00:41:32.870 because they are important.

NOTE Confidence: 0.7001029925

00:41:32.870 --> 00:41:34.186 And in many of these genes that

NOTE Confidence: 0.7001029925

00:41:34.186 --> 00:41:34.562 are important,

NOTE Confidence: 0.7001029925

00:41:34.570 --> 00:41:36.579 cancer are important in many other things

NOTE Confidence: 0.7001029925

00:41:36.579 --> 00:41:38.547 and that's exactly defined in this paper.

NOTE Confidence: 0.7001029925

00:41:38.550 --> 00:41:40.166 And this just shows you the numbers though.

NOTE Confidence: 0.7001029925

00:41:40.170 --> 00:41:42.658 So one or two step remove genes in

NOTE Confidence: 0.7001029925

00:41:42.658 --> 00:41:44.869 our genome is about 10,000 genes.

NOTE Confidence: 0.7001029925

00:41:44.870 --> 00:41:46.910 So actually probably the cancer 11

NOTE Confidence: 0.7001029925

00:41:46.910 --> 00:41:49.090 genes space is much much bigger,

NOTE Confidence: 0.7001029925

00:41:49.090 --> 00:41:50.978 just don't know about a lot of these

NOTE Confidence: 0.7001029925

00:41:50.978 --> 00:41:52.725 and of course they're importance is

NOTE Confidence: 0.7001029925

00:41:52.725 --> 00:41:55.810 not as important as a P53 mutation but

NOTE Confidence: 0.7001029925

00:41:55.810 --> 00:41:57.890 nevertheless they contributes very

NOTE Confidence: 0.7001029925

00:41:57.890 --> 00:42:01.189 likely contribute to the biological disease.

NOTE Confidence: 0.7001029925

00:42:01.190 --> 00:42:02.667 So where are you going with this?

NOTE Confidence: 0.7001029925

00:42:02.670 --> 00:42:05.015 So what you actually want to do

NOTE Confidence: 0.7001029925

00:42:05.015 --> 00:42:07.710 really is so address cancer as a

NOTE Confidence: 0.7001029925

00:42:07.710 --> 00:42:10.128 cellular transformation as as a a

NOTE Confidence: 0.7001029925

00:42:10.211 --> 00:42:13.028 defect in a in a in a complex system.

NOTE Confidence: 0.7001029925

00:42:13.030 --> 00:42:15.598 So complex systems fail through unique

NOTE Confidence: 0.7001029925

00:42:15.598 --> 00:42:18.250 combinations of individual non lethal events.

NOTE Confidence: 0.7001029925

00:42:18.250 --> 00:42:19.587 I mean just think about this if

NOTE Confidence: 0.7001029925

00:42:19.587 --> 00:42:21.064 you would run the statistics on

NOTE Confidence: 0.7001029925

00:42:21.064 --> 00:42:22.204 what's causing plane crashes,

NOTE Confidence: 0.7001029925

00:42:22.210 --> 00:42:23.254 even find anything.

NOTE Confidence: 0.7001029925

00:42:23.254 --> 00:42:24.994 Because even though flying through

NOTE Confidence: 0.7001029925

00:42:24.994 --> 00:42:26.309 a storm is a risk,

NOTE Confidence: 0.7001029925

00:42:26.310 --> 00:42:27.984 but many many planes fly through

NOTE Confidence: 0.7001029925

00:42:27.984 --> 00:42:29.782 storms have any problem, you know,

NOTE Confidence: 0.7001029925

00:42:29.782 --> 00:42:31.146 pilot sleeping or not.

NOTE Confidence: 0.7001029925

00:42:31.150 --> 00:42:31.800 Been trained,

NOTE Confidence: 0.7001029925

00:42:31.800 --> 00:42:34.075 it's a lot of happens that that

NOTE Confidence: 0.7001029925

00:42:34.075 --> 00:42:36.238 despite of this sort of human errors,

NOTE Confidence: 0.7001029925

00:42:36.240 --> 00:42:37.071 the plane survives,

NOTE Confidence: 0.7001029925

00:42:37.071 --> 00:42:38.733 you don't even know about it.

NOTE Confidence: 0.7001029925

00:42:38.740 --> 00:42:40.516 So it's really a unique combination

NOTE Confidence: 0.7001029925

00:42:40.516 --> 00:42:41.700 that brings down points.

NOTE Confidence: 0.7001029925

00:42:41.700 --> 00:42:43.359 And so that's the thing that we

NOTE Confidence: 0.7001029925

00:42:43.359 --> 00:42:45.177 actually try to see whether we could.

NOTE Confidence: 0.7001029925

00:42:45.180 --> 00:42:46.836 So some of these unique combination

NOTE Confidence: 0.7001029925

00:42:46.836 --> 00:42:47.940 of Germany and some

NOTE Confidence: 0.759412185238095

00:42:47.994 --> 00:42:49.961 of the events into a score and

NOTE Confidence: 0.759412185238095

00:42:49.961 --> 00:42:51.010 they ultimately visualize it.

NOTE Confidence: 0.759412185238095

00:42:51.010 --> 00:42:53.953 They did a little bit of a sort of

NOTE Confidence: 0.759412185238095

00:42:53.960 --> 00:42:55.760 preliminary kind of effort in this

NOTE Confidence: 0.759412185238095

00:42:55.760 --> 00:42:57.851 few years ago with wavey she trying

NOTE Confidence: 0.759412185238095

00:42:57.851 --> 00:42:59.790 to kind of map all the molecular

NOTE Confidence: 0.759412185238095

00:42:59.853 --> 00:43:01.949 abnormalities that particular cancer.

NOTE Confidence: 0.759412185238095

00:43:01.950 --> 00:43:04.118 As and visualize it in a standardized way

NOTE Confidence: 0.759412185238095

00:43:04.118 --> 00:43:06.763 in in these papers we try to resurrect

NOTE Confidence: 0.759412185238095

00:43:06.763 --> 00:43:08.963 this really delighted that Susan Coleman

NOTE Confidence: 0.759412185238095

00:43:08.963 --> 00:43:10.898 actually accepted this challenge for

NOTE Confidence: 0.759412185238095

00:43:10.898 --> 00:43:13.158 their hecaton in March next year.

NOTE Confidence: 0.759412185238095

00:43:13.158 --> 00:43:16.189 So we're going to lead A-Team to to

NOTE Confidence: 0.759412185238095

00:43:16.189 --> 00:43:18.990 try to develop this Kansas score. Umm.

NOTE Confidence: 0.903624126666667

00:43:21.920 --> 00:43:23.941 So the new classes of drugs, right.

NOTE Confidence: 0.903624126666667

00:43:23.941 --> 00:43:25.908 So that's the last piece that I'm

NOTE Confidence: 0.903624126666667

00:43:25.908 --> 00:43:27.807 actually going to talk to you a little

NOTE Confidence: 0.903624126666667

00:43:27.807 --> 00:43:29.588 bit because I'm so excited about it.

NOTE Confidence: 0.903624126666667

00:43:29.590 --> 00:43:30.970 So metabolically, right,

NOTE Confidence: 0.903624126666667

00:43:30.970 --> 00:43:34.190 rewiring is a major hallmark of cancers,

NOTE Confidence: 0.903624126666667

00:43:34.190 --> 00:43:35.588 yes. Yeah, we don't have any

NOTE Confidence: 0.903624126666667

00:43:35.588 --> 00:43:36.520 drugs that exploit it.

NOTE Confidence: 0.903624126666667

00:43:36.520 --> 00:43:38.104 So remember, a lot of chemotherapy

NOTE Confidence: 0.903624126666667

00:43:38.104 --> 00:43:39.472 drugs interfere with DNA synthesis

NOTE Confidence: 0.903624126666667

00:43:39.472 --> 00:43:41.278 because you need to double your DNA,

NOTE Confidence: 0.903624126666667

00:43:41.280 --> 00:43:42.968 but you need to also double your lipids.

NOTE Confidence: 0.903624126666667

00:43:42.970 --> 00:43:44.860 You also need to double your proteins.

NOTE Confidence: 0.903624126666667

00:43:44.860 --> 00:43:47.578 So why don't we have drugs in that space?

NOTE Confidence: 0.903624126666667

00:43:47.580 --> 00:43:50.205 So we started off with the computational

NOTE Confidence: 0.903624126666667

00:43:50.205 --> 00:43:51.969 biology project to look for.

NOTE Confidence: 0.903624126666667

00:43:51.970 --> 00:43:54.790 Most of isoenzyme diversity in cancer

NOTE Confidence: 0.903624126666667

00:43:54.790 --> 00:43:57.210 compared to corresponding normal tissue.

NOTE Confidence: 0.903624126666667

00:43:57.210 --> 00:44:00.333 So isoenzymes kind of more or less sort of

NOTE Confidence: 0.903624126666667

00:44:00.333 --> 00:44:02.672 could catalyze the same chemical reaction.

NOTE Confidence: 0.903624126666667

00:44:02.672 --> 00:44:05.059 But they are different genes and sometimes

NOTE Confidence: 0.903624126666667

00:44:05.059 --> 00:44:07.426 they are located in different compartments.

NOTE Confidence: 0.903624126666667

00:44:07.430 --> 00:44:09.290 So what you want to look at is is a

NOTE Confidence: 0.903624126666667

00:44:09.346 --> 00:44:11.736 particular isoenzyme becomes cancer dominant.

NOTE Confidence: 0.903624126666667

00:44:11.740 --> 00:44:14.064 So this isoenzyme diversity gets lost because

NOTE Confidence: 0.903624126666667

00:44:14.064 --> 00:44:16.660 out of the three or four isoforms that

NOTE Confidence: 0.903624126666667

00:44:16.660 --> 00:44:19.329 produce the same sort of chemical reaction,

NOTE Confidence: 0.903624126666667

00:44:19.330 --> 00:44:20.341 one becomes dominant.

NOTE Confidence: 0.903624126666667

00:44:20.341 --> 00:44:22.026 That may be actually important.

NOTE Confidence: 0.903624126666667

00:44:22.030 --> 00:44:22.274 Analogy.

NOTE Confidence: 0.903624126666667

00:44:22.274 --> 00:44:24.470 So if you're looking for is this sort of

NOTE Confidence: 0.903624126666667

00:44:24.525 --> 00:44:26.712 change that the normal cell has kind of fun,

NOTE Confidence: 0.903624126666667

00:44:26.720 --> 00:44:28.388 actually both sides of enzyme one

NOTE Confidence: 0.903624126666667

00:44:28.388 --> 00:44:30.310 and two and the cancer actually

NOTE Confidence: 0.903624126666667

00:44:30.310 --> 00:44:32.175 one of these becomes dominant.

NOTE Confidence: 0.903624126666667

00:44:32.180 --> 00:44:33.958 So we asked how many are these

NOTE Confidence: 0.903624126666667

00:44:33.958 --> 00:44:35.200 in the human genome?

NOTE Confidence: 0.903624126666667

00:44:35.200 --> 00:44:37.624 So we again went to the TTC share

NOTE Confidence: 0.903624126666667

00:44:37.624 --> 00:44:40.145 data and called all the human enzymes

NOTE Confidence: 0.903624126666667

00:44:40.145 --> 00:44:42.421 which have less than 5 isoforms

NOTE Confidence: 0.903624126666667

00:44:42.421 --> 00:44:45.309 to find to look for a pattern that

NOTE Confidence: 0.903624126666667

00:44:45.309 --> 00:44:46.666 showed this cancer dominance.

NOTE Confidence: 0.903624126666667

00:44:46.666 --> 00:44:47.994 Once we find this,

NOTE Confidence: 0.903624126666667

00:44:48.000 --> 00:44:50.052 then we looked whether we can see the same

NOTE Confidence: 0.903624126666667

00:44:50.052 --> 00:44:52.459 in the CLA the cancer cell line encyclopedia.

NOTE Confidence: 0.903624126666667

00:44:52.460 --> 00:44:53.908 Just to make sure that this is really

NOTE Confidence: 0.903624126666667

00:44:53.908 --> 00:44:54.930 happening at a cellular level,

NOTE Confidence: 0.903624126666667

00:44:54.930 --> 00:44:57.030 not at the tissue level because the

NOTE Confidence: 0.903624126666667

00:44:57.030 --> 00:45:00.026 TCG's tissue level and it also then

NOTE Confidence: 0.903624126666667

00:45:00.026 --> 00:45:02.098 once we confirm those that they are

NOTE Confidence: 0.903624126666667

00:45:02.098 --> 00:45:04.032 also dominant in a cancer cell line

NOTE Confidence: 0.903624126666667

00:45:04.032 --> 00:45:05.755 that enabled us to really check

NOTE Confidence: 0.903624126666667

00:45:05.755 --> 00:45:07.625 whether this particular isoform is,

NOTE Confidence: 0.903624126666667

00:45:07.630 --> 00:45:10.438 is survival critical in the depth

NOTE Confidence: 0.903624126666667

00:45:10.438 --> 00:45:13.050 map data which is CRISPR.

NOTE Confidence: 0.903624126666667

00:45:13.050 --> 00:45:14.580 You have no card database.

NOTE Confidence: 0.903624126666667

00:45:14.580 --> 00:45:16.695 And then the final hit you wanted to confirm,

NOTE Confidence: 0.903624126666667

00:45:16.700 --> 00:45:18.176 so this is what we found.

NOTE Confidence: 0.903624126666667

00:45:18.180 --> 00:45:22.085 So there are about 136 cancer breast cancer

NOTE Confidence: 0.903624126666667

00:45:22.085 --> 00:45:24.960 dominant isoenzymes that we find in the CG.

NOTE Confidence: 0.903624126666667

00:45:24.960 --> 00:45:27.102 About 81 of these are also cancer

NOTE Confidence: 0.903624126666667

00:45:27.102 --> 00:45:29.139 dominant in breast cancer cell lines,

NOTE Confidence: 0.903624126666667

00:45:29.140 --> 00:45:32.568 but 53 are important for survival.

NOTE Confidence: 0.903624126666667

00:45:32.568 --> 00:45:34.053 When you knock it out,

NOTE Confidence: 0.903624126666667

00:45:34.060 --> 00:45:36.610 you can sell lines, survival improves.

NOTE Confidence: 0.903624126666667

00:45:36.610 --> 00:45:38.270 And about 44 of these,

NOTE Confidence: 0.903624126666667

00:45:38.270 --> 00:45:40.184 the locking out the the particular

NOTE Confidence: 0.903624126666667

00:45:40.184 --> 00:45:42.080 isoform is more important than knocking

NOTE Confidence: 0.903624126666667

00:45:42.080 --> 00:45:44.336 out the other one and then you actually

NOTE Confidence: 0.903624126666667

00:45:44.389 --> 00:45:45.985 meet all these three criteria then

NOTE Confidence: 0.903624126666667

00:45:45.985 --> 00:45:48.751 you end up with about 17 potential

NOTE Confidence: 0.903624126666667

00:45:48.751 --> 00:45:51.586 targetable isoenzymes in breast cancer.

NOTE Confidence: 0.903624126666667

00:45:51.590 --> 00:45:53.662 But we did this for a whole bunch

NOTE Confidence: 0.903624126666667

00:45:53.662 --> 00:45:55.719 of cancer types and the the most

NOTE Confidence: 0.903624126666667

00:45:55.719 --> 00:45:57.713 shared sort of cancel them in a

NOTE Confidence: 0.903624126666667

00:45:57.713 --> 00:45:59.958 nicer form turned out to be a C1

NOTE Confidence: 0.903624126666667

00:45:59.958 --> 00:46:02.550 or acetyl coenzyme carboxylase.

NOTE Confidence: 0.903624126666667

00:46:02.550 --> 00:46:05.446 And this little uncertainty,

NOTE Confidence: 0.903624126666667

00:46:05.446 --> 00:46:08.795 the things the right side for

NOTE Confidence: 0.903624126666667

00:46:08.795 --> 00:46:10.370 you shows the

NOTE Confidence: 0.78179626

00:46:10.370 --> 00:46:12.274 the actual pattern expression pattern, right.

NOTE Confidence: 0.78179626

00:46:12.274 --> 00:46:14.859 So the red one is a potential target and the

NOTE Confidence: 0.78179626

00:46:14.859 --> 00:46:17.001 first column or the first sort of set by

NOTE Confidence: 0.78179626

00:46:17.060 --> 00:46:19.499 the line start is the normal tissue and the

NOTE Confidence: 0.78179626

00:46:19.499 --> 00:46:21.560 second column is the corresponding cancer.

NOTE Confidence: 0.78179626

00:46:21.560 --> 00:46:22.995 So you see that the blue goes

NOTE Confidence: 0.78179626

00:46:22.995 --> 00:46:24.309 down because it's lost in cancer,

NOTE Confidence: 0.78179626

00:46:24.310 --> 00:46:25.630 but then the red stays up.

NOTE Confidence: 0.78179626

00:46:25.630 --> 00:46:27.390 So we actually looked at why this is

NOTE Confidence: 0.78179626

00:46:27.390 --> 00:46:29.908 happening. It's maturation driven.

NOTE Confidence: 0.78179626

00:46:29.910 --> 00:46:31.248 And but what is a C?

NOTE Confidence: 0.78179626

00:46:31.250 --> 00:46:34.229 So C1 and C2 are actually the first literally

NOTE Confidence: 0.78179626

00:46:34.229 --> 00:46:36.788 the enzymes in fatty acid synthesis.

NOTE Confidence: 0.78179626

00:46:36.790 --> 00:46:38.795 They pre they are immediately

NOTE Confidence: 0.78179626

00:46:38.795 --> 00:46:41.530 before fast or fatty acid synthase.

NOTE Confidence: 0.78179626

00:46:41.530 --> 00:46:43.430 They convert acetyl coenzyme to

NOTE Confidence: 0.78179626

00:46:43.430 --> 00:46:45.774 Malaya coenzyme and this C1 is

NOTE Confidence: 0.78179626

00:46:45.774 --> 00:46:47.270 actually in the cytoplasm.

NOTE Confidence: 0.78179626

00:46:47.270 --> 00:46:49.070 C2 is the mitochondrial membrane

NOTE Confidence: 0.78179626

00:46:49.070 --> 00:46:50.870 also regulates fatty acid breakdown.

NOTE Confidence: 0.78179626

00:46:50.870 --> 00:46:52.550 So if you block ACC,

NOTE Confidence: 0.78179626

00:46:52.550 --> 00:46:56.084 you block fatty acid synthesis and

NOTE Confidence: 0.78179626

00:46:56.084 --> 00:46:58.440 accelerate fatty acid burning.

NOTE Confidence: 0.78179626

00:46:58.440 --> 00:47:00.421 So it turns out that actually this

NOTE Confidence: 0.78179626

00:47:00.421 --> 00:47:02.013 wasn't real skin of pharmaceutical

NOTE Confidence: 0.78179626

00:47:02.013 --> 00:47:04.077 companies for a long time because

NOTE Confidence: 0.78179626

00:47:04.077 --> 00:47:05.817 because as a target for Nash,

NOTE Confidence: 0.78179626

00:47:05.820 --> 00:47:09.438 which is non Alcoholics started

NOTE Confidence: 0.78179626

00:47:09.438 --> 00:47:11.804 hepatitis or fatty liver and it's also

NOTE Confidence: 0.78179626

00:47:11.804 --> 00:47:13.979 actually one of the major targets for

NOTE Confidence: 0.78179626

00:47:13.979 --> 00:47:16.160 herbicides that we use in agriculture.

NOTE Confidence: 0.78179626

00:47:16.160 --> 00:47:18.200 Turns out that Pfizer actually had a drug

NOTE Confidence: 0.78179626

00:47:18.200 --> 00:47:19.968 that worked amazingly well in people.

NOTE Confidence: 0.78179626

00:47:19.970 --> 00:47:22.322 They put it through several clinical trials

NOTE Confidence: 0.78179626

00:47:22.322 --> 00:47:24.598 and they established that it actually works,

NOTE Confidence: 0.78179626

00:47:24.600 --> 00:47:26.511 it blocks the novel fatty acid synthesis

NOTE Confidence: 0.78179626

00:47:26.511 --> 00:47:28.729 as you see on that curve that ports.

NOTE Confidence: 0.78179626

00:47:28.730 --> 00:47:31.172 The percent of the noble lipogenesis

NOTE Confidence: 0.78179626

00:47:31.172 --> 00:47:32.998 in people, it was also safe,

NOTE Confidence: 0.78179626

00:47:32.998 --> 00:47:34.006 except for one thing.

NOTE Confidence: 0.78179626

00:47:34.010 --> 00:47:36.020 It caused a little bit of

NOTE Confidence: 0.78179626

00:47:36.020 --> 00:47:37.360 hypertriglyceridemia and made and

NOTE Confidence: 0.78179626

00:47:37.416 --> 00:47:39.288 caused a drop in platelet counts.

NOTE Confidence: 0.78179626

00:47:39.290 --> 00:47:41.262 You know, we play the games on 400,000,

NOTE Confidence: 0.78179626

00:47:41.262 --> 00:47:42.378 so the politicians,

NOTE Confidence: 0.78179626

00:47:42.378 --> 00:47:44.402 not the 200,200 thousand is actually,

NOTE Confidence: 0.78179626

00:47:44.402 --> 00:47:45.464 it's a 50% drop.

NOTE Confidence: 0.78179626

00:47:45.464 --> 00:47:47.576 But we don't even count this as a

NOTE Confidence: 0.78179626

00:47:47.576 --> 00:47:48.869 toxicity in chemotherapy because

NOTE Confidence: 0.78179626

00:47:48.869 --> 00:47:50.484 it's a very safe level.

NOTE Confidence: 0.78179626

00:47:50.490 --> 00:47:50.894 Nevertheless,

NOTE Confidence: 0.78179626

00:47:50.894 --> 00:47:52.914 Pfizer felt that that this

NOTE Confidence: 0.78179626

00:47:52.914 --> 00:47:54.530 warrants discontinuing the drug.

NOTE Confidence: 0.78179626

00:47:54.530 --> 00:47:56.834 So we reached out to them and we actually

NOTE Confidence: 0.78179626

00:47:56.834 --> 00:47:58.737 got the right to test this drug.

NOTE Confidence: 0.78179626

00:47:58.740 --> 00:47:59.067 In.

NOTE Confidence: 0.78179626

00:47:59.067 --> 00:48:00.702 In preclinical models and hope

NOTE Confidence: 0.78179626

00:48:00.702 --> 00:48:03.539 to bring it back to the clinic if

NOTE Confidence: 0.78179626

00:48:03.539 --> 00:48:04.637 these little promising,

NOTE Confidence: 0.78179626

00:48:04.640 --> 00:48:08.399 but did the preclinical model look promising?

NOTE Confidence: 0.78179626

00:48:08.400 --> 00:48:10.626 So I don't really invitro data

NOTE Confidence: 0.78179626

00:48:10.626 --> 00:48:11.739 because the invitro,

NOTE Confidence: 0.78179626

00:48:11.740 --> 00:48:14.414 you know metabolism is highly sort of.

NOTE Confidence: 0.78179626

00:48:14.420 --> 00:48:15.704 Dependent on how much fatty acid

NOTE Confidence: 0.78179626

00:48:15.704 --> 00:48:17.399 and one that you have in the media.

NOTE Confidence: 0.78179626

00:48:17.400 --> 00:48:19.938 So this is the in vivo data in mice.

NOTE Confidence: 0.78179626

00:48:19.940 --> 00:48:22.060 So this is PBX to macros that we

NOTE Confidence: 0.78179626

00:48:22.060 --> 00:48:23.802 contracted out for Jackson lab and

NOTE Confidence: 0.78179626

00:48:23.802 --> 00:48:25.530 you see that this ACC inhibitor

NOTE Confidence: 0.78179626

00:48:25.586 --> 00:48:27.841 actually inhibits the growth although

NOTE Confidence: 0.78179626

00:48:27.841 --> 00:48:29.194 doesn't strike completely.

NOTE Confidence: 0.78179626

00:48:29.200 --> 00:48:31.960 The MDA MB 468 Genographic did here

NOTE Confidence: 0.78179626

00:48:31.960 --> 00:48:34.170 at Yale shows the same thing but the

NOTE Confidence: 0.78179626

00:48:34.170 --> 00:48:35.615 most striking thing was synergy,

NOTE Confidence: 0.78179626

00:48:35.620 --> 00:48:38.244 the doxorubicin and Vina Robin and

NOTE Confidence: 0.78179626

00:48:38.244 --> 00:48:40.464 also with the collaborator is

NOTE Confidence: 0.78179626

00:48:40.464 --> 00:48:42.240 interested endocrine sensitive CVD

NOTE Confidence: 0.78179626

00:48:42.305 --> 00:48:44.585 and resistance to develop the food.

NOTE Confidence: 0.78179626

00:48:44.590 --> 00:48:47.830 Strand resistant MCF 7 cell line,

NOTE Confidence: 0.78179626

00:48:47.830 --> 00:48:49.720 she also showing you know xenograft

NOTE Confidence: 0.78179626

00:48:49.720 --> 00:48:51.462 model that there are actually

NOTE Confidence: 0.78179626

00:48:51.462 --> 00:48:52.728 inhibited the growth.

NOTE Confidence: 0.78179626

00:48:52.730 --> 00:48:54.488 So this looks pretty promising to

NOTE Confidence: 0.78179626

00:48:54.488 --> 00:48:56.854 us and we do some additional studies

NOTE Confidence: 0.78179626

00:48:56.854 --> 00:48:59.486 to really figure out more about the

NOTE Confidence: 0.882094448666667

00:48:59.550 --> 00:49:01.430 synergy between chemotherapy agents and

NOTE Confidence: 0.882094448666667

00:49:01.430 --> 00:49:04.510 we hope to get this back from Pfizer.

NOTE Confidence: 0.882094448666667

00:49:04.510 --> 00:49:06.510 But how does this work?

NOTE Confidence: 0.882094448666667

00:49:06.510 --> 00:49:08.946 So the most interesting thing was that

NOTE Confidence: 0.882094448666667

00:49:08.946 --> 00:49:11.360 when we looked at what transcriptional

NOTE Confidence: 0.882094448666667

00:49:11.360 --> 00:49:14.391 changes occur after exposure to this drug,

NOTE Confidence: 0.882094448666667

00:49:14.400 --> 00:49:16.200 what really was.

NOTE Confidence: 0.882094448666667

00:49:16.200 --> 00:49:19.710 Striking is the that there was a

NOTE Confidence: 0.882094448666667

00:49:19.710 --> 00:49:21.930 dramatic increase in genes that are.

NOTE Confidence: 0.882094448666667

00:49:21.930 --> 00:49:24.865 Mediating and involved in unfolded

NOTE Confidence: 0.882094448666667

00:49:24.865 --> 00:49:27.213 protein response and upregulate

NOTE Confidence: 0.882094448666667

00:49:27.213 --> 00:49:29.160 endoplasmic reticulum stress.

NOTE Confidence: 0.882094448666667

00:49:29.160 --> 00:49:31.550 So our working hypothesis thereby

NOTE Confidence: 0.882094448666667

00:49:31.550 --> 00:49:33.940 inhibiting the Novo fattiest synthesis,

NOTE Confidence: 0.882094448666667

00:49:33.940 --> 00:49:36.005 you actually alter the membrane

NOTE Confidence: 0.882094448666667

00:49:36.005 --> 00:49:38.070 composition of the endoplasmic reticulum.

NOTE Confidence: 0.882094448666667

00:49:38.070 --> 00:49:41.177 You know proteins have to find a threat

NOTE Confidence: 0.882094448666667

00:49:41.177 --> 00:49:43.956 through the membrane to get into the

NOTE Confidence: 0.882094448666667

00:49:43.956 --> 00:49:45.609 endoplasmic reticulum for secondary

NOTE Confidence: 0.882094448666667

00:49:45.610 --> 00:49:48.070 modifications and we think that by

NOTE Confidence: 0.882094448666667

00:49:48.070 --> 00:49:50.178 changing the endoplasmic reticulum lipid

NOTE Confidence: 0.882094448666667

00:49:50.178 --> 00:49:52.208 composition we change this process.

NOTE Confidence: 0.882094448666667

00:49:52.210 --> 00:49:54.569 Of of protein synthesis and in user

NOTE Confidence: 0.882094448666667

00:49:54.569 --> 00:49:56.044 unfolded protein response which

NOTE Confidence: 0.882094448666667

00:49:56.044 --> 00:49:57.676 eventually overwhelms the cell.

NOTE Confidence: 0.882094448666667

00:49:57.680 --> 00:49:59.660 So that's the project that we do in the lab.

NOTE Confidence: 0.882094448666667

00:49:59.660 --> 00:50:01.598 Look at the lipid membrane composition

NOTE Confidence: 0.882094448666667

00:50:01.598 --> 00:50:03.884 of of the endoplasmic reticulum as as

NOTE Confidence: 0.882094448666667

00:50:03.884 --> 00:50:06.156 far as we can and the lipid alterations

NOTE Confidence: 0.882094448666667

00:50:06.156 --> 00:50:08.854 in the cells exposed to this and also

NOTE Confidence: 0.882094448666667

00:50:08.854 --> 00:50:10.935 some some reporter systems to nail

NOTE Confidence: 0.882094448666667

00:50:10.935 --> 00:50:12.957 this as the mechanism of action.

NOTE Confidence: 0.907215034285714

00:50:15.010 --> 00:50:17.929 So I'm going to summarize this really.

NOTE Confidence: 0.907215034285714

00:50:17.930 --> 00:50:19.685 So for those of you who are clinical fellows,

NOTE Confidence: 0.907215034285714

00:50:19.690 --> 00:50:20.965 you know every clinical dilemma

NOTE Confidence: 0.907215034285714

00:50:20.965 --> 00:50:22.910 that we discussed in a tumor boards,

NOTE Confidence: 0.907215034285714

00:50:22.910 --> 00:50:25.046 it's a research question asking for a study,

NOTE Confidence: 0.907215034285714

00:50:25.050 --> 00:50:26.290 some movies disheartened then

NOTE Confidence: 0.907215034285714

00:50:26.290 --> 00:50:28.150 people come about saying that OK,

NOTE Confidence: 0.907215034285714

00:50:28.150 --> 00:50:29.186 what should I research?

NOTE Confidence: 0.907215034285714

00:50:29.186 --> 00:50:30.481 I mean what you should

NOTE Confidence: 0.907215034285714

00:50:30.481 --> 00:50:31.589 research is all around us.

NOTE Confidence: 0.907215034285714

00:50:31.590 --> 00:50:33.347 You just need to open your eye.

NOTE Confidence: 0.907215034285714

00:50:33.350 --> 00:50:35.135 And so recognizing the prognostic

NOTE Confidence: 0.907215034285714

00:50:35.135 --> 00:50:36.920 importance of Pathologic CR residual

NOTE Confidence: 0.907215034285714

00:50:36.976 --> 00:50:38.661 disease has left new treatment

NOTE Confidence: 0.907215034285714

00:50:38.661 --> 00:50:40.346 strategies and improved survival in

NOTE Confidence: 0.907215034285714

00:50:40.398 --> 00:50:42.174 triple negative disease and her two

NOTE Confidence: 0.907215034285714

00:50:42.174 --> 00:50:44.652 positive disease and I showed you how so.

NOTE Confidence: 0.907215034285714

00:50:44.652 --> 00:50:46.267 Molecular offices of these issues

NOTE Confidence: 0.907215034285714

00:50:46.267 --> 00:50:47.947 also gives some idea that how

NOTE Confidence: 0.907215034285714

00:50:47.947 --> 00:50:50.160 we could make it even better by

NOTE Confidence: 0.907215034285714

00:50:50.160 --> 00:50:51.860 studying the difference between

NOTE Confidence: 0.907215034285714

00:50:51.860 --> 00:50:53.560 the nonresponders and responders.

NOTE Confidence: 0.907215034285714

00:50:53.560 --> 00:50:55.020 So immunotherapy established its

NOTE Confidence: 0.907215034285714

00:50:55.020 --> 00:50:57.210 value in breast cancer and Robinson

NOTE Confidence: 0.907215034285714

00:50:57.273 --> 00:50:59.463 is now approved as as neoadjuvant

NOTE Confidence: 0.907215034285714

00:50:59.463 --> 00:51:00.923 therapy together with chemotherapy

NOTE Confidence: 0.907215034285714

00:51:00.986 --> 00:51:02.596 for all three primary disease.

NOTE Confidence: 0.907215034285714

00:51:02.600 --> 00:51:04.586 It's also approved as first line

NOTE Confidence: 0.907215034285714

00:51:04.586 --> 00:51:06.900 therapy for PD like 1 positive

NOTE Confidence: 0.907215034285714

00:51:06.900 --> 00:51:08.277 metastatic breast cancer.

NOTE Confidence: 0.907215034285714

00:51:08.280 --> 00:51:10.450 And I think we have a reasonably

NOTE Confidence: 0.907215034285714

00:51:10.450 --> 00:51:12.636 decent explanation why you need the PD

NOTE Confidence: 0.907215034285714

00:51:12.636 --> 00:51:14.430 ligand one in the metastatic disease.

NOTE Confidence: 0.907215034285714

00:51:14.430 --> 00:51:16.425 So we are about to launch studies

NOTE Confidence: 0.907215034285714

00:51:16.425 --> 00:51:17.919 to demonstrate that similar benefit

NOTE Confidence: 0.907215034285714

00:51:17.919 --> 00:51:19.949 could be seen in a subset of

NOTE Confidence: 0.907215034285714

00:51:19.949 --> 00:51:21.110 molecular defined subset,

NOTE Confidence: 0.907215034285714

00:51:21.110 --> 00:51:23.826 small subset of ER positive breast cancers.

NOTE Confidence: 0.907215034285714

00:51:23.830 --> 00:51:25.672 And we also have some promising

NOTE Confidence: 0.907215034285714

00:51:25.672 --> 00:51:27.548 markers that could actually make this

NOTE Confidence: 0.907215034285714

00:51:27.548 --> 00:51:29.324 whole strategy safer and more cost

NOTE Confidence: 0.907215034285714

00:51:29.324 --> 00:51:30.913 effective by tailoring the treatment

NOTE Confidence: 0.907215034285714

00:51:30.913 --> 00:51:32.785 to those who really needed it.

NOTE Confidence: 0.907215034285714

00:51:32.790 --> 00:51:34.716 But these you need validations and

NOTE Confidence: 0.907215034285714

00:51:34.716 --> 00:51:37.121 I think the most exciting sort of

NOTE Confidence: 0.907215034285714

00:51:37.121 --> 00:51:39.233 things on the horizon clinically is

NOTE Confidence: 0.907215034285714

00:51:39.233 --> 00:51:41.277 CDN surveillance and interventional

NOTE Confidence: 0.907215034285714

00:51:41.277 --> 00:51:43.982 homophone macular relapse that might

NOTE Confidence: 0.907215034285714

00:51:43.982 --> 00:51:46.108 ultimately reduce further metastatic

NOTE Confidence: 0.907215034285714

00:51:46.108 --> 00:51:48.184 recurrences and this understanding

NOTE Confidence: 0.907215034285714

00:51:48.184 --> 00:51:50.779 the molecular phylogeny of metastatic

NOTE Confidence: 0.907215034285714

00:51:50.779 --> 00:51:53.014 disease really prompted this idea

NOTE Confidence: 0.907215034285714

00:51:53.014 --> 00:51:54.355 that because the.

NOTE Confidence: 0.907215034285714

00:51:54.360 --> 00:51:57.342 Synchronous mats are very similar to

NOTE Confidence: 0.907215034285714

00:51:57.342 --> 00:51:59.876 the primary tumors might be they are

NOTE Confidence: 0.907215034285714

00:51:59.876 --> 00:52:01.809 responding to the same way and the

NOTE Confidence: 0.907215034285714

00:52:01.809 --> 00:52:03.723 micro mats that remain after eradicating

NOTE Confidence: 0.907215034285714

00:52:03.723 --> 00:52:05.976 those are also similar to the to them.

NOTE Confidence: 0.907215034285714

00:52:05.980 --> 00:52:08.010 So that the microbes that remain after

NOTE Confidence: 0.907215034285714

00:52:08.010 --> 00:52:09.804 the primary tumor is being resected

NOTE Confidence: 0.907215034285714

00:52:09.804 --> 00:52:11.834 that may be approaching the same these

NOTE Confidence: 0.907215034285714

00:52:11.888 --> 00:52:13.784 disease with the same strategy that

NOTE Confidence: 0.907215034285714

00:52:13.784 --> 00:52:15.926 we very successfully used in stage

NOTE Confidence: 0.907215034285714

00:52:15.926 --> 00:52:18.554 three disease might actually cure a

NOTE Confidence: 0.907215034285714

00:52:18.554 --> 00:52:22.036 small subset maybe 10% maybe 30% of of

NOTE Confidence: 0.907215034285714

00:52:22.036 --> 00:52:24.790 the Novo metastatic stage four disease.

NOTE Confidence: 0.907215034285714

00:52:24.790 --> 00:52:25.243 And.

NOTE Confidence: 0.907215034285714

00:52:25.243 --> 00:52:27.508 There's a really deep portfolio

NOTE Confidence: 0.907215034285714

00:52:27.508 --> 00:52:29.910 of new classes of drugs.

NOTE Confidence: 0.907215034285714

00:52:29.910 --> 00:52:31.510 And that's my last slide.

NOTE Confidence: 0.907215034285714

00:52:31.510 --> 00:52:33.862 I apologize ahead of time for people who

NOTE Confidence: 0.907215034285714

00:52:33.862 --> 00:52:35.606 actually didn't make it to the slide,

NOTE Confidence: 0.907215034285714

00:52:35.610 --> 00:52:37.146 but I ran out of space.

NOTE Confidence: 0.907215034285714

00:52:37.150 --> 00:52:38.536 But these are the various people

NOTE Confidence: 0.907215034285714

00:52:38.536 --> 00:52:40.224 who worked in my lab and contributed

NOTE Confidence: 0.907215034285714

00:52:40.224 --> 00:52:41.876 the work that I showed you and

NOTE Confidence: 0.907215034285714

00:52:41.929 --> 00:52:43.417 students and other collaborators

NOTE Confidence: 0.907215034285714

00:52:43.417 --> 00:52:44.905 and collaborators within Yale.

NOTE Confidence: 0.8774344

00:52:50.630 --> 00:52:50.980 So.

NOTE Confidence: 0.876696786363636

00:53:02.110 --> 00:53:04.714 Yeah, so. If you have any

NOTE Confidence: 0.876696786363636

00:53:04.714 --> 00:53:06.800 questions then feel free to.

NOTE Confidence: 0.876696786363636

00:53:06.800 --> 00:53:10.170 Ask yes, silly. I have.

NOTE Confidence: 0.70466318

00:53:13.600 --> 00:53:14.860 Saying that, we were going to.

NOTE Confidence: 0.697274038

00:53:17.980 --> 00:53:21.016 And you mentioned, right and when you

NOTE Confidence: 0.697274038

00:53:21.016 --> 00:53:23.890 talked about the model especially.

NOTE Confidence: 0.697274038

00:53:23.890 --> 00:53:27.672 Negative. I want to know if you will

NOTE Confidence: 0.697274038

00:53:27.672 --> 00:53:30.478 consider rate in that model and it's so.

NOTE Confidence: 0.800806662666667

00:53:33.020 --> 00:53:35.414 So actually Kim and and some other

NOTE Confidence: 0.800806662666667

00:53:35.414 --> 00:53:37.575 previous lab members did they really

NOTE Confidence: 0.800806662666667

00:53:37.575 --> 00:53:39.705 nice analysis trying to see whether

NOTE Confidence: 0.800806662666667

00:53:39.705 --> 00:53:42.084 there is a immune difference between

NOTE Confidence: 0.800806662666667

00:53:42.084 --> 00:53:44.625 triple negative breast cancer by race.

NOTE Confidence: 0.800806662666667

00:53:44.625 --> 00:53:47.500 The hypothesis was that that.

NOTE Confidence: 0.800806662666667

00:53:47.500 --> 00:53:50.517 Stress and this sort of this weathering

NOTE Confidence: 0.800806662666667

00:53:50.517 --> 00:53:52.680 that that unfortunately many people

NOTE Confidence: 0.800806662666667

00:53:52.680 --> 00:53:55.062 with African American or Hispanic race

NOTE Confidence: 0.800806662666667

00:53:55.062 --> 00:53:57.492 have to suffer would have an impact

NOTE Confidence: 0.800806662666667

00:53:57.492 --> 00:53:59.173 on your immune immune system, right.

NOTE Confidence: 0.800806662666667

00:53:59.173 --> 00:54:01.037 So the truth is that if there is

NOTE Confidence: 0.800806662666667

00:54:01.037 --> 00:54:02.803 such a thing, it's really subtle.

NOTE Confidence: 0.800806662666667

00:54:02.803 --> 00:54:04.909 We find some some really intriguing

NOTE Confidence: 0.800806662666667

00:54:04.909 --> 00:54:06.788 things around macrophages things,

NOTE Confidence: 0.800806662666667

00:54:06.790 --> 00:54:08.956 but whether this really holds up,

NOTE Confidence: 0.800806662666667

00:54:08.960 --> 00:54:10.140 I'm not quite sure yet.

NOTE Confidence: 0.800806662666667

00:54:10.140 --> 00:54:11.771 So I can send you the slides

NOTE Confidence: 0.800806662666667

00:54:11.771 --> 00:54:13.230 and we have some things,

NOTE Confidence: 0.800806662666667

00:54:13.230 --> 00:54:15.358 some references there and we we see

NOTE Confidence: 0.800806662666667

00:54:15.358 --> 00:54:17.699 some things but I'm not sure that it's.

NOTE Confidence: 0.800806662666667

00:54:17.700 --> 00:54:18.495 It's really detectable.

NOTE Confidence: 0.800806662666667

00:54:18.495 --> 00:54:20.350 There are other things that we haven't

NOTE Confidence: 0.800806662666667

00:54:20.397 --> 00:54:21.972 looked at but we plan to do which is

NOTE Confidence: 0.800806662666667

00:54:21.972 --> 00:54:23.650 like inflammatory markers in the blood.

NOTE Confidence: 0.800806662666667

00:54:23.650 --> 00:54:25.560 But that's also kind of

NOTE Confidence: 0.800806662666667

00:54:25.560 --> 00:54:26.706 biased by comorbidities.

NOTE Confidence: 0.800806662666667

00:54:26.710 --> 00:54:28.510 So if you have a lot of other diseases,

NOTE Confidence: 0.800806662666667

00:54:28.510 --> 00:54:30.390 then it's just going to be high anyway.

NOTE Confidence: 0.800806662666667

00:54:30.390 --> 00:54:32.148 And in terms of the models,

NOTE Confidence: 0.800806662666667

00:54:32.150 --> 00:54:32.892 you know,

NOTE Confidence: 0.800806662666667

00:54:32.892 --> 00:54:35.118 so Pathologic CI is equally good

NOTE Confidence: 0.800806662666667

00:54:35.118 --> 00:54:37.544 in terms of metastatic recurrence

NOTE Confidence: 0.800806662666667

00:54:37.544 --> 00:54:39.146 regardless of race.

NOTE Confidence: 0.800806662666667

00:54:39.150 --> 00:54:39.766 In fact,

NOTE Confidence: 0.800806662666667

00:54:39.766 --> 00:54:41.614 I personally have a really serious

NOTE Confidence: 0.800806662666667

00:54:41.614 --> 00:54:43.397 doubt that there is any major

NOTE Confidence: 0.800806662666667

00:54:43.397 --> 00:54:44.912 genetic sort of explanation

NOTE Confidence: 0.800806662666667

00:54:44.912 --> 00:54:47.640 behind disparities and outcome.

NOTE Confidence: 0.793267928888889

00:54:50.390 --> 00:54:52.694 So models that include in survival

NOTE Confidence: 0.793267928888889

00:54:52.694 --> 00:54:54.325 rates are problematic, right,

NOTE Confidence: 0.793267928888889

00:54:54.325 --> 00:54:56.700 because it perpetuated a risk

NOTE Confidence: 0.793267928888889

00:54:56.700 --> 00:54:58.925 factor that that maybe not true.

NOTE Confidence: 0.793267928888889

00:54:58.925 --> 00:54:59.985 So if your social,

NOTE Confidence: 0.793267928888889

00:54:59.990 --> 00:55:03.290 social circumstances change.

NOTE Confidence: 0.793267928888889

00:55:03.290 --> 00:55:05.690 Is there a question from online?

NOTE Confidence: 0.793267928888889

00:55:05.690 --> 00:55:06.760 I should call you back.

NOTE Confidence: 0.701762791666667

00:55:11.020 --> 00:55:13.708 So there's this question online that.

NOTE Confidence: 0.701762791666667

00:55:13.710 --> 00:55:16.924 Umm. Somebody's relevant regretting

NOTE Confidence: 0.701762791666667

00:55:16.924 --> 00:55:18.472 their choice that they're not breast

NOTE Confidence: 0.701762791666667

00:55:18.472 --> 00:55:19.588 oncologist and they agree with that.

NOTE Confidence: 0.701762791666667

00:55:19.590 --> 00:55:21.738 That's the do patients with inflammatory

NOTE Confidence: 0.701762791666667

00:55:21.738 --> 00:55:24.015 breast cancer have higher response rates

NOTE Confidence: 0.701762791666667

00:55:24.015 --> 00:55:26.361 to checkpoint inhibition and the agent

NOTE Confidence: 0.701762791666667

00:55:26.361 --> 00:55:28.289 setting regardless to applying results.

NOTE Confidence: 0.701762791666667

00:55:28.290 --> 00:55:29.350 Yeah, that's a good one.

NOTE Confidence: 0.701762791666667

00:55:29.350 --> 00:55:30.434 So you know inflammatory

NOTE Confidence: 0.701762791666667

00:55:30.434 --> 00:55:31.789 breast cancer is a misnomer.

NOTE Confidence: 0.701762791666667

00:55:31.790 --> 00:55:33.698 It's really, it's a clinical description

NOTE Confidence: 0.701762791666667

00:55:33.698 --> 00:55:35.649 that people came up and whatever

NOTE Confidence: 0.701762791666667

00:55:35.649 --> 00:55:37.486 maybe the 19th century and because

NOTE Confidence: 0.701762791666667

00:55:37.486 --> 00:55:38.976 the breast looks like inflamed,

NOTE Confidence: 0.701762791666667

00:55:38.980 --> 00:55:42.164 it's red and hot and and and swollen,

NOTE Confidence: 0.701762791666667

00:55:42.170 --> 00:55:44.172 it looks like a skin infection and

NOTE Confidence: 0.701762791666667

00:55:44.172 --> 00:55:45.950 very often primary care physicians.

NOTE Confidence: 0.701762791666667

00:55:45.950 --> 00:55:48.030 Give it antibiotics and it just gets worse.

NOTE Confidence: 0.701762791666667

00:55:48.030 --> 00:55:49.494 So inflammatory breast cancer

NOTE Confidence: 0.701762791666667

00:55:49.494 --> 00:55:51.324 actually is not particularly rich.

NOTE Confidence: 0.701762791666667

00:55:51.330 --> 00:55:54.378 In fact it's pretty poor in immune cells.

NOTE Confidence: 0.701762791666667

00:55:54.380 --> 00:55:55.361 But we did.

NOTE Confidence: 0.701762791666667

00:55:55.361 --> 00:55:56.996 Actually the first whole genome

NOTE Confidence: 0.701762791666667

00:55:56.996 --> 00:55:59.268 sequencing of inflammatory breast cancer,

NOTE Confidence: 0.701762791666667

00:55:59.270 --> 00:56:01.170 hoping to find something and

NOTE Confidence: 0.701762791666667

00:56:01.170 --> 00:56:03.290 disappointed we didn't find

NOTE Confidence: 0.701762791666667

00:56:03.290 --> 00:56:05.940 anything that actually defined this

NOTE Confidence: 0.701762791666667

00:56:05.940 --> 00:56:08.330 autonomically at the DNA sequence space,

NOTE Confidence: 0.701762791666667

00:56:08.330 --> 00:56:09.986 but we find some interesting things.

NOTE Confidence: 0.701762791666667

00:56:09.990 --> 00:56:12.534 Again, TGF beta macrophage

NOTE Confidence: 0.701762791666667

00:56:12.534 --> 00:56:15.718 related markers show up there.

NOTE Confidence: 0.701762791666667

00:56:15.720 --> 00:56:17.202 As potentially contributing

NOTE Confidence: 0.701762791666667

00:56:17.202 --> 00:56:19.178 to the poor outcome.

NOTE Confidence: 0.701762791666667

00:56:19.180 --> 00:56:19.760 But yeah,

NOTE Confidence: 0.701762791666667

00:56:19.760 --> 00:56:20.920 so inflammatory breast cancer

NOTE Confidence: 0.701762791666667

00:56:20.920 --> 00:56:22.810 is all the four subtypes and

NOTE Confidence: 0.701762791666667

00:56:22.810 --> 00:56:24.560 as far as we can tell today,

NOTE Confidence: 0.701762791666667

00:56:24.560 --> 00:56:26.485 there is really no proton

NOTE Confidence: 0.701762791666667

00:56:26.485 --> 00:56:27.640 nomical genomic alteration.

NOTE Confidence: 0.839109910666667

00:56:31.010 --> 00:56:32.765 So what type of preventive

NOTE Confidence: 0.839109910666667

00:56:32.765 --> 00:56:34.520 interventions do you foresee for

NOTE Confidence: 0.839109910666667

00:56:34.584 --> 00:56:36.489 patients with high cancer score.

NOTE Confidence: 0.839109910666667

00:56:36.490 --> 00:56:40.134 So if you already have validated and

NOTE Confidence: 0.839109910666667

00:56:40.134 --> 00:56:42.310 really effective prevention drugs,

NOTE Confidence: 0.839109910666667

00:56:42.310 --> 00:56:45.088 right, the moxen aromatase inhibitors and

NOTE Confidence: 0.839109910666667

00:56:45.088 --> 00:56:48.260 food and other drugs, the I type drugs,

NOTE Confidence: 0.839109910666667

00:56:48.260 --> 00:56:50.932 but they have side effects and and I

NOTE Confidence: 0.839109910666667

00:56:50.932 --> 00:56:53.404 think one way to use these cancer score

NOTE Confidence: 0.839109910666667

00:56:53.481 --> 00:56:55.897 would be to if you're high risk that

NOTE Confidence: 0.839109910666667

00:56:55.897 --> 00:56:57.970 you are close to this tipping point,

NOTE Confidence: 0.839109910666667

00:56:57.970 --> 00:56:59.050 I should say you that we

NOTE Confidence: 0.839109910666667

00:56:59.050 --> 00:56:59.770 don't have that score.

NOTE Confidence: 0.839109910666667

00:56:59.770 --> 00:57:00.598 It's working on it.

NOTE Confidence: 0.839109910666667

00:57:00.598 --> 00:57:02.129 But it's the idea that if you

NOTE Confidence: 0.839109910666667

00:57:02.129 --> 00:57:03.319 can tell that these biopsy,

NOTE Confidence: 0.839109910666667

00:57:03.320 --> 00:57:05.078 tissue biopsy shows that you are

NOTE Confidence: 0.839109910666667

00:57:05.078 --> 00:57:06.812 close to this tipping point and

NOTE Confidence: 0.839109910666667

00:57:06.812 --> 00:57:08.312 maybe you are willing to put

NOTE Confidence: 0.839109910666667

00:57:08.312 --> 00:57:09.739 up with some additional.

NOTE Confidence: 0.839109910666667

00:57:09.740 --> 00:57:10.280 Umm.

NOTE Confidence: 0.839109910666667

00:57:10.280 --> 00:57:12.980 Discomfort from a prevention drug.

NOTE Confidence: 0.764090394

00:57:17.620 --> 00:57:20.024 All right. Let's go ahead, Andrew.

NOTE Confidence: 0.764090394

00:57:20.024 --> 00:57:22.688 A lot of times with the

NOTE Confidence: 0.764090394

00:57:22.688 --> 00:57:24.969 people who have even PCR,

NOTE Confidence: 0.764090394

00:57:24.970 --> 00:57:27.268 they can relapse in the brain.

NOTE Confidence: 0.764090394

00:57:27.270 --> 00:57:29.130 And people sort of say that's

NOTE Confidence: 0.764090394

00:57:29.130 --> 00:57:30.950 due the blood brain barrier,

NOTE Confidence: 0.764090394

00:57:30.950 --> 00:57:33.915 but are there molecular alterations

NOTE Confidence: 0.764090394

00:57:33.915 --> 00:57:37.750 that predict frame labs or can you?

NOTE Confidence: 0.764090394

00:57:37.750 --> 00:57:39.436 No, I can't. But you know,

NOTE Confidence: 0.764090394

00:57:39.440 --> 00:57:40.483 I mean, that's the reason why I

NOTE Confidence: 0.764090394

00:57:40.483 --> 00:57:41.698 don't go to many of the meetings,

NOTE Confidence: 0.764090394

00:57:41.700 --> 00:57:43.270 because there are so many

NOTE Confidence: 0.764090394

00:57:43.270 --> 00:57:44.526 interesting things to study.

NOTE Confidence: 0.764090394

00:57:44.530 --> 00:57:47.306 I just enjoy them more but yeah so,

NOTE Confidence: 0.764090394

00:57:47.310 --> 00:57:49.443 so people tried that but they didn't find it.

NOTE Confidence: 0.764090394

00:57:49.450 --> 00:57:51.106 But what you bring up is illegal one right.

NOTE Confidence: 0.764090394

00:57:51.110 --> 00:57:53.049 So the pathologic CR is really good

NOTE Confidence: 0.764090394

00:57:53.049 --> 00:57:55.183 but it's not a perfect predictor and

NOTE Confidence: 0.764090394

00:57:55.183 --> 00:57:57.476 for for there are many reasons why

NOTE Confidence: 0.764090394

00:57:57.476 --> 00:57:59.654 there should be a disconnect with

NOTE Confidence: 0.764090394

00:57:59.654 --> 00:58:01.384 Pathologic CR improvement in survival.

NOTE Confidence: 0.764090394

00:58:01.384 --> 00:58:03.286 So you can't cure people twice.

NOTE Confidence: 0.764090394

00:58:03.290 --> 00:58:04.730 So if you enroll a lot of people

NOTE Confidence: 0.764090394

00:58:04.730 --> 00:58:06.070 that are on stage one breast

NOTE Confidence: 0.764090394

00:58:06.070 --> 00:58:07.468 cancer and the surgeon cure them,

NOTE Confidence: 0.764090394

00:58:07.470 --> 00:58:09.000 it doesn't really matter whether

NOTE Confidence: 0.764090394

00:58:09.000 --> 00:58:10.530 they are chemosensitive or not.

NOTE Confidence: 0.764090394

00:58:10.530 --> 00:58:12.778 But in terms of recurrences look to Silver

NOTE Confidence: 0.764090394

00:58:12.778 --> 00:58:15.130 Point out something that many oncologists.

NOTE Confidence: 0.764090394

00:58:15.130 --> 00:58:16.258 Even breast oncologists may

NOTE Confidence: 0.764090394

00:58:16.258 --> 00:58:17.668 not be totally familiar with.

NOTE Confidence: 0.764090394

00:58:17.670 --> 00:58:19.896 So there are a number of studies

NOTE Confidence: 0.764090394

00:58:19.896 --> 00:58:21.984 that show now that the first

NOTE Confidence: 0.764090394

00:58:21.984 --> 00:58:24.102 sight of recurrence of the PCR,

NOTE Confidence: 0.764090394

00:58:24.110 --> 00:58:26.196 half of the time it's the brain.

NOTE Confidence: 0.764090394

00:58:26.200 --> 00:58:28.916 When you have no PCR residual disease,

NOTE Confidence: 0.764090394

00:58:28.920 --> 00:58:31.013 then the brain is the first site

NOTE Confidence: 0.764090394

00:58:31.013 --> 00:58:32.978 in about 10% and it goes along

NOTE Confidence: 0.764090394

00:58:32.978 --> 00:58:34.580 with this idea that the brain

NOTE Confidence: 0.764090394

00:58:34.638 --> 00:58:36.228 is somehow a protected site.

NOTE Confidence: 0.764090394

00:58:36.230 --> 00:58:38.407 And the question is then how they

NOTE Confidence: 0.764090394

00:58:38.407 --> 00:58:40.654 actually can break this protection and

NOTE Confidence: 0.764090394

00:58:40.654 --> 00:58:42.744 really help avoid brain recurrences.

NOTE Confidence: 0.764090394

00:58:42.750 --> 00:58:44.580 There are some some really good

NOTE Confidence: 0.764090394

00:58:44.580 --> 00:58:46.656 initiatives in the in the her two

NOTE Confidence: 0.764090394

00:58:46.656 --> 00:58:48.511 positive space and some of the ADC

NOTE Confidence: 0.764090394

00:58:48.568 --> 00:58:50.810 may get in there triple 90 disease,

NOTE Confidence: 0.764090394

00:58:50.810 --> 00:58:53.010 but what actually would define

NOTE Confidence: 0.764090394

00:58:53.010 --> 00:58:55.391 high risk for brain recurrence

NOTE Confidence: 0.764090394

00:58:55.391 --> 00:58:57.766 in terms of molecular markers?

NOTE Confidence: 0.764090394

00:58:57.770 --> 00:59:00.426 But they could find that in a reproducible

NOTE Confidence: 0.764090394

00:59:00.426 --> 00:59:02.847 and accepted sort of widely accepted way.

NOTE Confidence: 0.9430172

00:59:06.360 --> 00:59:09.036 Thank you. Thank you for all

NOTE Confidence: 0.9430172

00:59:09.036 --> 00:59:11.618 of you who have joined both

NOTE Confidence: 0.9430172

00:59:11.620 --> 00:59:12.956 in person and virtually.

NOTE Confidence: 0.9430172

00:59:12.956 --> 00:59:15.402 This concludes our breast cancer

NOTE Confidence: 0.9430172

00:59:15.402 --> 00:59:16.906 awareness month grand rounds.

NOTE Confidence: 0.9430172

00:59:16.910 --> 00:59:17.590 Thank you so much.

NOTE Confidence: 0.53831303

00:59:38.790 --> 00:59:41.000 Yeah.