Today we have two speakers and our first speaker is Michaela Dine-in, who's an associate professor Epidemiology and Co leader of the Yale Cancer Center Cancer Prevention and Control Research program. She joined us from Duke University last year and is a Health Sciences features researcher specializing in using epidemiological methodologies to study complex datasets with particular expertise and leveraging existing real-world datasets to examine cancer outcomes.
Is also a leading researcher lean, and then I NCI funded study looking at health disparities in patients with kidney cancer. And so I think we’ll hear about some of that today.

Great, just pulling up my slides here. OK, looks like we’re ready to rock and roll. Alright so thank you so much. Good afternoon everyone.

I’m actually in Chicago right now and attending the Astro annual meeting. So technically it’s still morning here, but either way I’m delighted to
be speaking with you today so.

Uhm, as was mentioned, I'm a health outcomes researcher by training and I can bucket my current research projects into three broad categories, including emerging technology in oncology, survivorship, and patient outcomes and molecular oncology outcomes research.

But the running theme throughout these example projects is leveraging real-world data to answer questions about dissemination outcomes, costs and disparities, and how I think about answering...
these types of questions using real-world data resources. So what is the value added? Of health outcomes research and while RCT's are considered higher up in the food chain than cohort and case control studies in the traditional levels of evidence pyramid shown here, there are many types of questions that are not feasible to examine in the context of a trial, but that are feasible within health outcomes, study methodologies, and here are some examples of the types of questions we can answer about emerging diagnostics and therapeutics
00:02:09.144 --> 00:02:11.160 using real-world data resources.

00:02:11.160 --> 00:02:12.800 Randomized trials are required.

00:02:12.800 --> 00:02:15.260 Approval of a novel therapeutic agent,

00:02:15.260 --> 00:02:17.230 but approvals of diagnostics and

00:02:17.230 --> 00:02:19.200 other biomarkers are more complex

00:02:19.230 --> 00:02:21.168 and not always evaluated by ARC.

00:02:21.170 --> 00:02:23.425 Prior to their approval or

00:02:23.425 --> 00:02:24.778 coverage by insurance.

00:02:24.780 --> 00:02:27.230 However, even for therapeutic agents,

00:02:27.230 --> 00:02:29.590 initial approvals often arise from

00:02:29.590 --> 00:02:31.950 RCT comparisons with another single

00:02:32.025 --> 00:02:34.150 treatment which may be outdated

00:02:34.150 --> 00:02:36.275 by the time approvals received.

00:02:36.280 --> 00:02:37.106 In reality,

00:02:37.106 --> 00:02:38.758 more and more cancers.
Have increasing numbers of possible treatment options and combinations and it’s just not feasible to examine all possible strategies in a head-to-head fashion, and oftentimes there’s honestly not adequate financial incentives to support such trials. We also know that patients who participate in RCT’s differ systematically from the average real world patient, where life and treatment is just a lot messier as compared to the highly curated patient population and controlled environment of an RCT. And this is an example study,
not mine of a patient of patients

with primary CNS lymphoma treated at the same institution who received the same treatment both on and off protocol, and the investigators showed that patients who were treated in the real world practice meaning off protocol. Or older, sicker had worse disease and had dramatically worse survival than the patients who were treated on the clinical trial. So here I have presented an overview of many different types of data that can be used to conduct
real-world health outcomes research,
and what I really want to drive home is that it’s important to remind folks
that there is no perfect single data set. But by leveraging the major strengths
and weaknesses of different data, different types of datasets as they currently exist,
or improving upon them, we can answer some pretty cool questions. So this is an example of
a past fully completed study that I conducted in breast cancer, and this was a five year study that was funded by AHRQ.
Where we were looking at adoption,
chemotherapy, use and costs associated with Oncotype DX, in breast and breast cancer and a lot has changed in the subsequent years since this work was completed, but at the time in CC and guidelines. Recommended consideration of chemotherapy and all of early stage disease patients with primary tumors greater than one centimeter node. Negative ER positive disease, and patients characteristics that were consistent with chemotherapy. Candidacy and uncle Type DX was still relatively new to the scene at this time,
and no one had looked at its use in real world population.

So let’s consider the gaps in knowledge that existed at the time, so we know that randomized trials had confirmed the prognostic and predictive value of Oncotype DX, and there had been some single institution series that suggested that decreased chemotherapy was associated with archetype DX use. However, there hadn’t been any nationally representative studies conducted. There were still questions about whether
00:04:53.212 --> 00:04:55.535 or not the adoption and diffusion of
00:04:55.535 --> 00:04:57.497 Archetype DX was being done equitably
00:04:57.497 --> 00:04:59.916 across different subgroups in the population,
00:04:59.920 --> 00:05:01.045 and there are questions about
00:05:01.045 --> 00:05:01.720 the impact that.
00:05:01.720 --> 00:05:03.628 Architect DX was having on chemotherapy,
00:05:03.630 --> 00:05:04.440 utilizations and costs.
00:05:04.440 --> 00:05:05.520 In the real world.
00:05:05.520 --> 00:05:07.696 And finally,
00:05:07.696 --> 00:05:09.238 there was limited data on patients
00:05:09.240 --> 00:05:11.180 who are 65 years and older.
00:05:11.180 --> 00:05:14.090 in any of the child data.
00:05:14.090 --> 00:05:16.036 So in thinking about the types of
00:05:16.036 --> 00:05:17.158 questions about architects that
I was interested in looking at, I chose to use the seer Medicare linked data, which combines the detailed clinical pathologic data from this year registry with the LOGITUDINAL claims from the Medicare data. So we use the Medicare claims portion of the SEER Medicare data to detect the use of Oncotype DX in our study population. Now, there was no specific CPT procedure code for Oncotype DX. In fact, the test is build using the CPT code 84999. Defined as unlisted chemistry procedure. However,
using the knowledge that all Oncotype DX tests are processed by single provider in a single location, we were able to use an algorithm to detect the archetypes DX code in the Medicare claims data and confirm that all tests were performed by the same single provider from the same single location with 95% of these tests having identical payment of $3414. So this was considered a very creative approach at the time.
this creative approach is what got the study funded, but I’ve seen this approach recreated for other diagnostics many times signs. And this is just a side note to suggest that if you can think of novel ways to use data that have been around a long time, you can still make real contributions to the field. Interestingly, the Seer Medicare data now actually includes the Oncotype DX rescored data in the data set itself, so we were only able to detect.
00:06:42.599 --> 00:06:43.888 receipt of testing at the time,

00:06:43.890 --> 00:06:45.994 but did not know what the test results.

00:06:46.000 --> 00:06:48.168 Actually were so we were able to show

00:06:48.168 --> 00:06:50.156 that archetype decks used in the real

00:06:50.156 --> 00:06:51.960 world increased over the study period,

00:06:51.960 --> 00:06:54.192 particularly with in the younger age

00:06:54.192 --> 00:06:56.720 group in the SEER Medicare data.

00:06:56.720 --> 00:06:58.488 And since the use of Oncotype DX was

00:06:58.488 --> 00:07:00.232 supposed to inform whether or not

00:07:00.232 --> 00:07:01.480 a patient received chemotherapy,

00:07:01.480 --> 00:07:03.448 we wanted to see how often the the

00:07:03.448 --> 00:07:05.449 use of diagnostic or sorry we wanted

00:07:05.449 --> 00:07:08.081 to see how the use of the diagnostic

00:07:08.081 --> 00:07:10.325 was impacting the use of chemotherapy.

00:07:10.330 --> 00:07:11.930 And here we can see that in patients

NOTE Confidence: 0.921729892222222
who would traditionally be considered high risk due to their tumor size or stage, that chemotherapy. He's appeared to decline following the introduction of architect Deacs. So in multivariable analysis, we did not see an overall association between receipt of Archetype DX and receipt of chemo. However, we did see that patients with clinical markers of more aggressive disease such as tumor size, grade and NCCN, defined clinical pathologic risk had an increased likelihood of receiving chemo.
The most nuanced and interesting finding, however, was that when we looked at the interaction between receipt of Oncotype DX and NCCN defined clinical risk, we saw that. Receipt of Oncotype DX was associated with decreased chemo in NCCN high risk patients and increased chemo and NCCN low risk patients. So at the time it was a foregone conclusion by many that the use of Oncotype DX would not only be cost effective, but also costs saving.
there was a meta analysis of the ability of AC type DX to reduce costs, and it revealed that there was a wide range in the perceived benefit cost benefits of archetype deacs according to weather. A study had been funded by Genomic Health. The sponsor, which is those studies, are shown in blue on this graph. As opposed to other funding sources. So interestingly, the five studies that suggested Archetype DX was cost saving were all funded by genomic health. Ultimately, however,
these were all modeling studies and we wanted to try to look at real-world data, so this is important, because when you look closely at these modeling studies, 18 of them assume that T stage and tumor grade had no impact on chemotherapy decisions, which we clearly saw in the data and only five studies. Accounting for the fact that architect at DX testing might actually increase chemotherapy use
in clinically low risk patients.

So what did we find when we looked at costs associated with Oncotype DX in the real world setting?

So the main takeaway lesson was that the impact of these tests depends strongly on the patient population and pretest likelihood that a patient was going to get chemotherapy anyway. However, for lower intermediate patients, there is no evidence that Oncotype DX will reduce costs in actuality.
And it’s use is actually associated with higher non cancer costs, likely due to just general overall increased health care utilization in this population. And then finally using these same data, we were able to look at questions regarding what physician or provider characteristics were associated with the use of archetype DX and what we saw was that about 70% of patients who were receiving Oncotype DX had the Oncotype DX test ordered by their medical oncologists. But we were also able to look at
factors physician characteristics

that were associated with increased likelihood of receiving Oncotype DX and these were having been seen by a surgical oncologist having been seen having had your surgery at an academic Medical Center. Having been treated by a female medical oncologist and having been treated by a medical oncologist who was within five years of finishing their training. So I’m going to move on to my next example, which is from my current NCI funded R 01 where we are examining access and adherence to oral anti cancer agents and drivers of real world
disparities in patients with metastatic renal cell carcinoma.

As is the case in many cancers, the number of available therapies for kidney cancers have expanded dramatically over the past decade and a half and interestingly, ten of these therapies approved between 2005 and 2016. Of those 10, seven of them were oral agents and we can use real world data to look at issues pertaining to patients’ ability to access and then stay adherent to these potentially lifesaving drugs.
So once again, let’s take a look at what was known versus the knowledge gaps surrounding a use in patients with kidney cancer at the time. So we know we knew that oral anti-cancer agents and we know that they pose unique challenges to delivery and also there was clinical trial data that showed increased progression, free survival and overall survival typically always have shown to have a more favorable toxicity profile than traditional cytotoxic chemotherapies. However their continued.
To be gaps in the knowledge around whether outcomes, what outcomes and toxicities looked like in older and comorbid patient populations, there were few head-to-head OA comparisons and there were additional unknown adherence barriers as well as impacts of out of pocket costs on adherence and how the impact of nonadherence had on outcomes for these patients. So for this study, we once again decided to leverage the strengths of the Seer,
Medicare and the Medicare claims data, and in this case, Medicare Part D, which includes prescription drug claims, was crucial for this study. But we also added an additional data source called the North Carolina Cypher data. This is an example of a state cancer registry that’s been linked to claims data, and in this case it’s the North Carolina Cancer Registry data that has been linked to Medicare, Medicaid, and Blue Cross Blue Shield data. So you can see here. That strengths include the same detailed clinical pathologic data that’s
contained in the SEER Medicare data set.

But for patients of all ages, we receive Medicare is limited to those who are 65 years and older and with unsafe Cypher has patients with different types of insurance coverage. Where senior Medicare is limited, obviously, to just the Medicare population. So here I show the seer Medicare rates of utilization of oral anti cancer agents in patients with renal cell carcinoma and we also reproduce this data in the North Carolina cypher where we saw highly similar trajectories and rates of OH agents.
We found that roughly 1/3 of patients were receiving an oral anti-cancer agent at all within a year of being diagnosed with advanced disease and that the majority of these patients were initially treated with sunitinib. A multivariable analysis of CR Medicare factors associated with utilization did not show evidence of differential receipt of oral therapies by patient race, ethnicity, or socioeconomic status. However, we did see decreased utilization in patients who were unmarried, older, or that lived in the South. So one of the strengths of the
North Carolina cipher data is that it includes adults of all ages as well as private insurance. As I've already mentioned before, we adjusted for age. There were large differences in utilization by private versus Medicare insurance. However, in multivariable adjusted analysis, we saw that there was no difference in the utilization by insurance. Instead, this was likely driven entirely by age, with older patients being less likely to receive therapy. We also observed that frailty and...
00:14:10.246 --> 00:14:11.890 having multiple kohram abilities
NOTE Confidence: 0.915946695666667
00:14:11.958 --> 00:14:13.578 were both associated with.
NOTE Confidence: 0.915946695666667
00:14:13.580 --> 00:14:14.988 Decrease to a utilization.
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00:14:14.988 --> 00:14:17.482 And lastly we looked at patients with
NOTE Confidence: 0.915946695666667
00:14:17.482 --> 00:14:19.736 all stages of kidney cancer and saw
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00:14:19.736 --> 00:14:21.917 that patients who were diagnosed with
NOTE Confidence: 0.915946695666667
00:14:21.917 --> 00:14:24.131 stage one disease but that experienced
NOTE Confidence: 0.915946695666667
00:14:24.140 --> 00:14:26.090 progression to metastatic disease were
NOTE Confidence: 0.915946695666667
00:14:26.090 --> 00:14:28.490 less likely to utilize Inoue within
NOTE Confidence: 0.915946695666667
00:14:28.490 --> 00:14:30.788 a year of metastatic disease diagnosis,
NOTE Confidence: 0.915946695666667
00:14:30.790 --> 00:14:33.275 and this is likely due to slower
NOTE Confidence: 0.915946695666667
00:14:33.275 --> 00:14:35.564 growing disease with a less urgent
NOTE Confidence: 0.915946695666667
00:14:35.564 --> 00:14:37.096 need to treat immediately.
NOTE Confidence: 0.915946695666667
00:14:37.100 --> 00:14:39.086 Come for oral anti cancer agents.
NOTE Confidence: 0.915946695666667
00:14:39.090 --> 00:14:39.426 However,
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00:14:39.426 --> 00:14:41.106 it's important to remember that
in addition to utilization, there's also the concept of adherence or the percentage of time a patient was taking their anti cancer drug. We know that in general, adherence to oral medications is often far from 100% due to any number of reasons such as side effects or costs. We looked at adherence in both the Seer Medicare and the Cypher cohorts and we observed slightly higher rates of adherence within the North Carolina cypher patient population. As compared to the CR Medicare cohort, we think this is largely due to the
difference in age between the cohorts.
As both cohorts showed evidence of either older patients or those with Medicare insurance having lower adherence rates.
North Carolina Cypher was somewhat limited in power due to the smaller sample sizes, and it did not examine adherence by different agents in the multivariable analysis.
However, there was evidence of substantially lower adherence to soften it in both cohorts.
We saw a strong impact of poverty on adherence within the SEER Medicare data, but not the North Carolina cypher data.
And although it is unclear why,
we hypothesize that older patients living on a fixed income may be more sensitive to financial stressors. Consistent with this, we saw that OAS, with out of pocket costs over $200, were associated with decreased adherence within the SEER Medicare cohort. So these real world datasets also allow you to look at survival. And here is a three month landmark survival curve of all ‘cause mortality for a pass. Open abusers by whether they received the trial. Recommended dose of 800 milligrams of
pheasant per day in the three months following a initiation for the patients getting the prescribed dose for the first three months of treatment, we saw superior outcomes and survival was assessed beginning at three months post postoperative initiation. In order to avoid introducing Immortal time bias in the analysis. So I think it’s incredibly critical to acknowledge that a key limitation of all these data sets is that the patient perspective and the patient voice is missing. I also feel it’s incredibly important to do our best to include this perspective, even when working exclusively.
with secondary data, and one way that we address this for the renal cell carcinoma.
A study was by partnering with patient advocacy groups who helped us identify questions that were most important to them. So, for example, these patients and their families, they wanted to know how often providers were switching their medications. Which is something we hadn’t planned on examining,
So we looked at the request of the patients, and we found that while only 6% of RCC patients switched away within 90 days of diagnosis, that number increased to 20% of RCC patients switched to their always within one year of diagnosis.

So now I’d like to move on to an example of current future work that I’m doing. I was recently awarded a Cancer Society 5 year Research Scholar Grant and this grant will be developing algorithms to inform risk stratified care for long term cancer survivors. This figure was modified from a paper by Effinger and McCabe which...
00:17:48.343 --> 00:17:50.770 shows at the top the current model, care for cancer survivors, which is more of a one size fits all approach.

00:17:55.330 --> 00:17:57.245 Once the patient is diagnosed with their cancer, their care is transferred to an oncologist for an indefinite period of time.

00:18:00.444 --> 00:18:02.110 Little to no ongoing participation from the PCP.

00:18:02.110 --> 00:18:03.902 The bottom shows the proposed shared practice model care based on risk stratification, which helps to inform the point in time when a
cancer survivors care might be
appropriately transferred back to you or
shared with the primary care physician
with the idea being that the new
model represents both a more efficient
and better quality model of care.
So this figure is from a study
where McConnell and colleagues used
National Cancer Registry data from
the UK and Northern Ireland tourist
stratify patients with twenty of
the most common cancers into three
groups based on overall survival at
one in five years from diagnosis.
And this is just to demonstrate that
crude risk categorization is possible
and is currently being used to inform treatment in other countries. So the authors noted that important caveats of this analysis included the absence of treatment information which was not available, and. That their data was unable to assess treatment related complications, both of which I propose to improve upon in our models for this ACS grant. So once again, we return to existing currently existing knowledge gaps, existing real-world data and outcome methodologies can help to address,
so we know that Uncle logic and
noncaloric risks vary substantially by
cancer stage and treatment and cancer type.
We also know that cancer site
and stage alone can provide broad
uncle logic risk categories.
However, non uncle logic disease.
Risks have been defined qualitatively,
but not quantitatively,
and stage alone can provide broad
uncle logic risk categories.
However, non uncle logic disease.
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uncle logic risk categories.
However, non uncle logic disease.
Risks have been defined qualitatively,
Medicare and the North Carolina cipher data.
But the new data set addition to this project will be incorporating data from the Veterans Health system and the overarching plan is to use inputs that are available from all three of these datasets, such as cancer or specific variables like site and stage treatment. Personal characteristics like age and gender and race and ethnicity, and then aging related concerns like comorbidities and functional status to develop risk prediction models.
prostate and colorectal cancers.

To predict both ankle logic and non oncologic events, for which long term cancer survivors are at increased risk.

So these risk algorithm algorithms will separate long term cancer survivors into low, medium and high risk categories to help inform discussions between survivors and physicians about their optimal care going forward and ultimately the final product will be a freely available web calculator in which patients and or physicians can input their individual information to help categorize their individual
risk and inform pathways of care.

So next on the horizon for me is tackling additional unmet needs of traditional health services research through novel data linkages and I’m developing studies that will include actual physical tumor samples so that we can run genomic sequence analysis on them and then link that additional biologic information to both tumor registry data and longitudinal claims data. So there are a couple existing resources which I have already tapped into to get this.
work off the ground and the first of which is the SEER residual tissue repository, which is a program that used to be funded by NCI to maintain physical tumor samples for patients contained in the SEER registry for three participating sites, which were Iowa, Hawaii and Los Angeles, CA. So like I said, the program consists of pathologic specimens. These are old specimens were collected between 1992 and 2006. I've already. Mention the participating see registries, but they do allow the ability to physically analyze tumor samples and So what I did was we recently completed a
proof of concept study on a very small breast cancer cohort to demonstrate the process for combining the sear, the Medicare, and the genomic or biologic data obtained from running gene expression analysis on the tumor samples themselves. So unfortunately, LA did not participate in this pilot study due to an inability to procure large enough funds to cover their participation. Costs and this left us with two very distinct and racially and ethnically homogeneous populations which were not ideal.
We would have liked it to have been much more representative, but it did allow us to proceed with the proof of concept study and here is a brief summary of some of our major findings, so this publication is in press and will be published in two days in JAMA Network and I'm happy to share that publication with folks to go through in more detail once it's published. But you can see that our major findings really show how we were able to leverage the different aspects of these three different data linkages. The three different datasets that we linked together so we were able
to show from the Medicare claims data that symptomatic detection of breast cancer was associated with a higher mortality hazards ratio as from the SEER registry data. We were able to show that.

Low levels of high school graduation rates were associated with a higher mortality hazard ratio and then from the tumor samples and the genetic analysis that we conducted on these, we were able to show that androgen receptor macrophage set of toxicity and T. Rex signaling were all associated with reduced mortality.
But the key thing that I want to highlight here is that factors related to socioeconomic status and screening access remained associated with mortality even after adjusting for clinical and genomic factors.

So what does the future look like for this work?

Well, I’m getting ready to submit a narrow one which would leverage the sear virtual tissue repository and proposes the first in kind linkage ever of the tumor samples with ceron, Medicare longitudinal claims.

So the server consists of
seven participating.

See registry, so we’re up to 7 from 3, and the pathologic specimen location is known for the most recent 10 years.

So this is, this is the oldest. The tissue samples are ten years old. But the collection is ongoing, so these are recent tissues.

And once again we must physically request and fund the acquisition of the pathologic specimens from the pathology labs storing them.

But what are we proposing to do? We’re calling this a retro genomic approach, which we are defining as a combination.

49
00:24:25.189 --> 00:24:27.263 of population level cohort studies
NOTE Confidence: 0.916855962
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00:24:31.563 --> 00:24:33.358 which to pursue genomic analysis,
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00:24:42.898 --> 00:24:44.952 we can use the Medicare claims data
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00:24:46.800 --> 00:24:49.120 interest and then go and pull the tumor
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00:24:49.120 --> 00:24:50.898 samples for the patients who experience
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00:24:50.898 --> 00:24:52.866 these outcomes in the real world
NOTE Confidence: 0.916855962
00:24:52.866 --> 00:24:54.970 and study which treatment patterns,
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00:24:54.970 --> 00:24:55.830 SES factors,
or clinical pathologic characteristics appear to be driving those outcomes. And in the case of RRCC proposal, that we’re getting ready to submit in February, February, we’re going to look at two rare events experienced by patients related to amino therapy. Namely, severe IO toxicities and durable responders, so we’re calling this project the virtual siert issue, registry Genomics and Medicare cohort, or a Verge cohort. And as I mentioned,
our first application to go in renal cell carcinoma since this study will be following on the heels of my current R 01, but our intention always has been and remains to have several different bridge cohorts across different disease sites. Answering all types of different clinical questions. So in summary, there are many questions relevant to cancer care that can be informed and enhanced by real World Health services research. Many questions cannot be feasibly or ethically addressed by clinical trials alone,
and novel linkages may pave the way to novel opportunities in health services research.

There are several datasets that are available for research in real world outcomes data and each data has its own strengths, weaknesses, and nuances that you need to know how to work with in order to get the best. And most accurate data and then the incorporation of genomics and biology into health service research is on the horizon. With that,
I want to thank the team members who participated in all the various studies that I presented today. All of the work I do is team-based science and I couldn’t do it without the clinical collaborators and the support staff who are helping me with this work. Thank you for your time.

Thank you Michaela. Very interesting work. If there are any questions, I guess what we do is we type them into the chat. While we’re waiting now to question. I thought the most interesting thing he showed was the effect of ZIP code. The five fold increase in mortality.
Yes, ’cause of course in within the ZIP code there are many people. There’s a range of educational levels, so if you just actually broke it down. Are you able to break it down by actual, whether or not a patient has graduated or not? ’cause I would assume then that difference would be much greater. Yeah, I mean, so obviously that would be ideal. That’s just that’s just a limitation of this year Medicare data, of the the SES data is in this available in their Medicare data,
and I could talk a whole another half hour about this. Is zipcode level information, so it’s not ideal, but it does give you a sense of you. You get zipcode level information about high school graduation, about poverty. Uhm, like the racial or ethnic makeup of a neighborhood somebody lives in. So obviously it’s a proxy. It’s not ideal, but it’s better than what’s in a lot of other datasets, so it’s still
Despite those very striking differences.

We have a question from Laos.

Yes, Titan, congratulations.

What you described, I wonder who is your year collaborator Co-investigator for the genomic analysts piece of it, who will actually do the sequencing and data analysts and linking to the clinical data.

Yeah, so we're still working through the details of that, but we've been talking to all the various cores and thinking about...
exactly what we want to do in terms of the genomic analysis. Obviously there’s a couple things that are going to weigh in. This is a big study. It like I said, it’s going to involve. It’s all ecipes from all of the six registries I mentioned are all on board. We’re going to have, so that’ll be six sites, and so a lot of this unfortunately is gonna be driven by what we can afford in terms of, you know. So we’re going to start with a very focused analysis and then from there you know.
I’m hoping to build on that with either administrative supplements or other funding mechanisms to build out and expand on that, so that’s still that specific pieces build still being in development right now, but we’re. Talking with all the Yale course. There’s a lot to follow up with you because you know, I couldn’t write the Yale Genetics Genomics program and you may know that we have a similar large initiative that’s run by like Murray. The generations project,
00:29:02.910 --> 00:29:04.368 and I think there is a lot of synergy
NOTE Confidence: 0.734202074444445
00:29:04.370 --> 00:29:05.577 that you could you could leverage.
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00:29:05.577 --> 00:29:07.059 Yeah, it’d be great to talk,
NOTE Confidence: 0.734202074444445
00:29:07.060 --> 00:29:08.315 and we’re still we’re still
NOTE Confidence: 0.734202074444445
00:29:08.315 --> 00:29:09.319 developing that specific piece.
NOTE Confidence: 0.734202074444445
00:29:09.320 --> 00:29:10.336 I would love to talk about it more.
NOTE Confidence: 0.86150755
00:29:12.280 --> 00:29:15.115 Thanks Flash any other questions or comments?
NOTE Confidence: 0.828124807692308
00:29:18.950 --> 00:29:22.088 How the work is obviously critically
NOTE Confidence: 0.828124807692308
00:29:22.088 --> 00:29:25.809 dependent on how good the datasets are.
NOTE Confidence: 0.828124807692308
00:29:25.810 --> 00:29:27.754 Which you have not a lot of control over
NOTE Confidence: 0.828124807692308
00:29:27.754 --> 00:29:29.436 other than select which ones to use.
NOTE Confidence: 0.828124807692308
00:29:29.440 --> 00:29:31.828 I mean for example other VA.
NOTE Confidence: 0.828124807692308
00:29:31.830 --> 00:29:32.856 How does that compare to see?
NOTE Confidence: 0.828124807692308
00:29:32.860 --> 00:29:34.477 Or how does that compare to Medicare?
NOTE Confidence: 0.828124807692308
00:29:34.480 --> 00:29:36.570 Or are there systematic differences?
NOTE Confidence: 0.932014826
00:29:36.930 --> 00:29:38.730 Yeah, so great question.
Again, I have a whole other talk just talking specifically about these. Uhm, so you know it. It’s all about knowing the datasets well knowing what their strengths or weaknesses are and knowing how to leverage them specifically for the wrist ratification grant that I’m talking about where we’re going to be using serum, Medicare cipher and the VA data, we’re specifically focusing on the variables of interest on things that we know we can get out of. Each of those three datasets, right?
So because we want to be able to develop and then validate the risk prediction algorithms. I mean, I said it from the beginning. There's no perfect data set. Medicare data. It is probably the most widely used real-world data set for oncology. Specific research is an incredibly strong data set, but the two big limitations that everyone can tell you right off the top of their head is that it's limited to those who are 65 years and older.
It’s Medicare only, and then the other limitation is there’s a pretty significant lag with the data because it relies on a linkage that’s done every two years at NCI, so it’s usually about three to four years behind, right? So if you’re trying to look at emerging technologies, it can be a little bit of a nuisance. So from the current R 01. Actually getting ready to purchase a cohort of the Medicare 100% data. So the limitation to that data set
is going to be that it doesn’t have the seer registry information, so we’re not going to know things like stage or like other clinical pathologic variables. However, the whole you know we’re trying to fill in the gaps that we know exist from the previous work that we did with the other datasets, which is the lag that we saw in this era. Medicare data and the North Carolina cipher data, so we can’t look at O as in the context of current immunotherapy, which we know is playing a huge role.
In a renal cell carcinoma treatment right now, so the Medicare claims data, while it will have different gaps, is going to allow us to look at other questions alongside of what we’ve already done to look at how aydelette OAA utilization and adherence looks in the context of amino therapies. So it’s just about figuring out, like it’s just about acknowledging where the limitations exist, and then figuring out a way to kind of fill that information in. Terrific,
thank you very much.

Very interesting talk.

We need to move on to our second speaker who's Gloria Wong and Gloria is a social professor of OBGYN

and reproductive sciences here, and she specialized in the treatment and prevention of ovarian, uterine, and cervical cancers. She’s a board certified gynecological oncologist who performs minimally invasive surgery and her research interests are in Dimitriou.

SIS associated and ovarian cancer in the prevention and treatment of endometrial cancer recurrence.
So Gloria, the floor is yours.

Hey, thank you so much for the introduction and I really enjoyed the first talk and learnt a lot.

Let me just see if I can bring up my slides here. Can you see those? Yes, could you put in presentation? Yes perfect.

Well today I wanted to talk about a couple of topics near and dear to my heart, which is translational science and pivotal trials in gynecological cancer. I have my disclosures on file with the CME office, none of which are related.
In this talk, I want to first give an epidemiological overview of the epidemiology and current trends in GYN cancer. Challenges and successes in the field of GYN Cancer Research, including highlighting some recent practice-changing trials and how translational science in my personal experience can be a driver for clinical trial development and team science. And then also just touch briefly on some resources available for translational research. And these are the learning objectives.
Endometrial cancer has been increasing in both incidence and mortality in the United States. Currently, the lifetime risk of developing under mutual cancer is about one in 32 and over 800,000 women in the US are living with endometrial cancer. Ovarian cancer mortality has slightly declined in recent years and currently the lifetime risk of developing ovarian cancer is about one in 83 and over 200,000 women in EU S. Thanks to HPV vaccination and cervical screening.
The cervical cancer rate has declined over the past decades to about 167 women. However, there are significant disparities related to access of care and affecting outcomes. Cancers arise from the reproductive tract organs, including the ovary, fallopian tube, uterus, cervix, and vagina, and these organs are remarkable in their ability to respond rapidly to endocrine signals, produce sex hormones and their remarkable capacity for proliferation, regeneration, and morphological changes.
and some of these do relate to underlying risk factors and protective factors for GY and cancers. Full fearing cancer, there’s a correlation with increased lifetime ambulatory cycles, whereas oral contraceptive use, pregnancy and risk, and breastfeeding decrease risk. Term line genetic testing has become much more widespread and may, be available to the general public. It is available now for out of pocket cost for you know about $250.
to determine if one carries a BRCA one or two mutation and for those patients risk reducing surgery is highly protective for women at average risk. There is a benefit to opportunistic salpingectomy so, a surgical removal of the tubes at the time of other pelvic surgery for benign indications. Endometrial cancer is linked to the rising obesity rate unopposed estrogen as well as hereditary factors, and we know that use of progestin containing oral contraceptive can offer
00:36:30.732 --> 00:36:33.365 protection as well as risk reducing
00:36:33.365 --> 00:36:36.173 surgery for patients at higher risk.
00:36:36.180 --> 00:36:40.879 And cervical cancer can be really
00:36:40.879 --> 00:36:46.140 eliminated with widespread implementation
00:36:46.140 --> 00:36:49.175 of HPV vaccination and cervical screening,
00:36:49.175 --> 00:37:01.686 and I’m going to focus today on and a
00:37:01.686 --> 00:37:04.460 mutual cancer which has an increasing
00:37:04.460 --> 00:37:07.432 incidence and mortality rate as well
00:37:07.432 --> 00:37:10.624 as substantial racial disparity in outcomes.
00:37:10.630 --> 00:37:11.144 However,
00:37:11.144 --> 00:37:14.228 this is buffeted by recent successes
and pivotal trials in GI and cancer in just in the past 18 months alone, we've seen new first line maintenance therapy options for ovarian cancer. New indications for immunotherapy, including for mismatch repair, proficient at a mutual cancer, as well as new first line and second line standard of care for cervical cancer. So really quite amazing how many. Pivotal trials have resulted in the recent 18 to 24 months leading to practice changing. Approaches, so in 2000 end of 2019 the results of Primon Paolo one were published.
00:37:58.434 --> 00:38:00.899 in the New England Journal,
NOTE Confidence: 0.863152505882353
00:38:00.900 --> 00:38:03.609 leading to the approval of two different
NOTE Confidence: 0.863152505882353
00:38:03.609 --> 00:38:05.872 options for first line maintenance
NOTE Confidence: 0.863152505882353
00:38:05.872 --> 00:38:08.447 therapy of epithelial ovarian cancer.
NOTE Confidence: 0.863152505882353
00:38:08.450 --> 00:38:10.110 Fallopian tube for primary piratini,
NOTE Confidence: 0.863152505882353
00:38:10.110 --> 00:38:12.170 oh cancer. Following complete or
NOTE Confidence: 0.863152505882353
00:38:12.170 --> 00:38:14.916 partial response to first line platinum
NOTE Confidence: 0.863152505882353
00:38:14.916 --> 00:38:18.900 based chemotherapy, the new rap rib.
NOTE Confidence: 0.863152505882353
00:38:18.900 --> 00:38:21.660 Demonstrated a significant improvement
NOTE Confidence: 0.863152505882353
00:38:21.660 --> 00:38:25.316 in progression free survival in both
NOTE Confidence: 0.863152505882353
00:38:25.316 --> 00:38:28.004 the overall intent to treat population
NOTE Confidence: 0.863152505882353
00:38:28.004 --> 00:38:30.227 and the homologous recombination
NOTE Confidence: 0.863152505882353
00:38:30.227 --> 00:38:33.935 deficient population with a hazard risk
NOTE Confidence: 0.863152505882353
00:38:33.935 --> 00:38:38.840 of 0.43 in progression free survival.
NOTE Confidence: 0.863152505882353
00:38:38.840 --> 00:38:42.608 Come with clear divergence of the
NOTE Confidence: 0.863152505882353
progression free survival curves.

Similarly, Palo one which tested elapp rib and bevacizumab for first line maintenance, showed remarkable improvement and progression.

Mutated population hazard ratio of 0.31 and on the lower right. Patients without a BRAC mutation. But with a molecular test demonstrating.

Homologous recombination deficiency as tested by genomic instability also showed a progression free survival benefit with a hazard ratio of 0.4. And outcomes for patients who,
unfortunately often prevent present with advanced stage ovarian cancer, and we know that upon recurrence becomes more difficult to treat and more likely to be chemo resistant.

In mutual cancer, just to review some of our recent exciting new options. And this has been really a big deal because actually progress has been quite slow and endometrial cancer. Progestin therapy Megace was approved. You know, many decades ago for palliative treatment of enemy,

enemy, troll, and breast cancer. However, really many decades
elapsed without any new trials,
NOTE Confidence: 0.784302386363636

new indicate indicated therapies for endometrial cancer of a big benefit
NOTE Confidence: 0.784302386363636

for our patients without mutual cancer,
NOTE Confidence: 0.784302386363636

with seen with the accelerated approval of pembrolizumab.
NOTE Confidence: 0.784302386363636

For a minute, solid tumors that were mismatch repair deficient as about
NOTE Confidence: 0.784302386363636

20% of endometrial cancers are, or microsatellite instability
NOTE Confidence: 0.784302386363636

high or more recently,
NOTE Confidence: 0.784302386363636

with the addition of the accelerated approval for the tumor mutation burden high.
NOTE Confidence: 0.784302386363636

Uhm?
NOTE Confidence: 0.784302386363636

Tumors more recently this.
NOTE Confidence: 0.784302386363636

Here we have an additional
option for mismatch repair

deficient and demetral cancer,

just Starla Mob,

which received accelerated approval

in August and then most recently

the keynote 775 updated results were

presented at ESMO following previous

showing actually with this combination.

Of pembrolizumab and lymphatic nib.

Showing actually with this combination.

In proficient mismatch repair.

Proficient endometrial cancers.

Uhm,

an improvement in overall survival,

leading to regular approval of

79
this combination for patients with endometrial cancer that is not MSI high that is mismatch repair proficient and have disease progression following prior systemic therapy. Next, I want to move into how we, as clinicians scientists, participate. And a example for trial in progress that I’d like to share. So I have a couple of different projects moving into clinical trials. This one that’s currently in enrolling in clinical trial. And emerged from what began as a collaborative team science project, funded by a narrow one and then
another trial, which I’m in the process of moving towards the clinic, which was based on translational science done in my lab. Supported by DoD grant. For this study, which began quite a long time ago, UM, I collaborated with, UM, Epidemia Cancer epidemiology experts, and we wanted to ask the question of what could, what we know about the development of endometrial cancer and how obesity is a major risk factor.
for Type 1 endometrial cancer
NOTE Confidence: 0.868508536666667
which has been increasing steadily
NOTE Confidence: 0.868508536666667
and underlies the primary.
NOTE Confidence: 0.868508536666667
Increase in the endometrial cancer
NOTE Confidence: 0.868508536666667
incidence as shown here in this graph.
NOTE Confidence: 0.781636
See. A man is dorceau tick tick
NOTE Confidence: 0.781636
tick lining rate of hysterectomy
NOTE Confidence: 0.781636
is another contributing factor.
NOTE Confidence: 0.781636
And for many studies,
NOTE Confidence: 0.781636
including prospective study of
NOTE Confidence: 0.781636
the Women’s Health Initiative,
NOTE Confidence: 0.781636
that some of the underlying biological
NOTE Confidence: 0.781636
mechanisms linking obesity to endometrial
NOTE Confidence: 0.781636
cancer include increased estrogen
NOTE Confidence: 0.781636
levels increased by availability of
00:43:58.584 --> 00:44:01.156 estrogens and insulin resistance.

00:44:01.160 --> 00:44:04.256 Uhm, and the question that we asked was, do these factors that underlie the development of endometrial cancer.

00:44:04.260 --> 00:44:07.422 Do they play a role in the recurrence and progression of women diagnosed with endometrial cancer?

00:44:09.530 --> 00:44:12.813 For this study, we utilized the tissue by repository of the GOT 210 study. This is a study that was over 60 sites around the USFRGOG Gynaecologic oncology group sites, now under the auspices of NRG Oncology and enrolled patients who...
00:44:40.700 --> 00:44:42.660 were undergoing standard surgical
treatment for endometrial cancer and
prospective specimen banking was.
00:44:48.242 --> 00:44:50.664 Performed and sent to a
centralized tissue bank,
00:44:51.620 --> 00:44:54.676 the jioji tissue bank.
00:44:57.585 --> 00:44:59.730 And prospective epidemiological
surveys and outcomes.
00:45:01.825 --> 00:45:03.920 Treatment and outcomes data was
obtained in order to facilitate
translational research,
00:45:08.995 --> 00:45:11.775 including a variety of molecular
and genetic genomic assays.
00:45:13.650 and data integration.
00:45:21.380 So we proposed a study
within this G210 cohort,
which we obtained funding for, and this focused on the patients who had endometrioid Histology, and we investigated the sex hormone insulin like growth factor, signaling pathways implicated in the development of endometrial cancer, to determine if these factors. More related to the recurrence or progression of higher risk and a study included over 800 women, of whom 35% experienced a recurrence in a follow-up of over five years.
The models were adjusted for known clinical risk factors of recurrence, including age, stage and grade, which were all significant risk factors for recurrence and just to summarize, some of the interesting findings which we presented at an ASCO plenary and we published this year in cancer epidemiol AMPDCEP. We found that circulating estradiol is positively associated with recurrence risk, independent of other factors, and in addition, a particular tissue biomarker that I was interested in based on some of my laboratory research that phosphorylated...
expression of insulin receptor,

IGF one receptor was also independently associated with recurrence risk.

And this is an example of immunohistochemical staining for the phosphorylated activated form of the receptor.

Because of the, you know, large number of patients we did utilize high throughput approaches for this study, which included construction of tissue microarrays and.

And in real time PCR. So the translational impact of these findings is that we identified novel sex hormone and insulin,
IGF axis tissue and circulating biomarkers of recurrence in a prospective study of high stage endometrial cancer and this led to a motivation to test strategies to target these pathways for prevention and treatment of endometrial cancer and endometrial cancer recurrence.

Come in my lab. We looked at different potential therapies for treating metastatic cancer that could be superior to the previously used strategies. So the most commonly used strategies in the past have been protesting agents aromat ACE inhibitors or
combination tamoxifen and megace, and all of those. Resulted in really modest efficacy with progression. Free survivals even in the first line setting of around three months, so this indicated a need for more effective. Effective approaches for endocrine therapy and we found both in cell line models demonstrate we found that combination cyclin D kinase CDK 46 inhibition with AROMATISSE inhibitors was potently synergistic and endometrial cancer cell lines and this is. Something that it’s been very
successfully implemented.

Of course, in estrogen receptor positive breast cancer.

And this just shows in vivo data of showing on the Y axis the tumor volumes of the endometrial cancer xenograft.

As expected, we found that RB mutant mutual cancers are not responsive to this combination and you could see in the red that the combination therapy was significantly superior to either agent alone and.

Both and much was really able to inhibit growth of this aggressive
endometrial cancer xenografted and this is work we presented at the AACR meeting.

And this led me to initiate a collaboration guided by valuable input from, you know my division colleagues here at Yale, who of course are leading clinical researchers as well as colleagues incorporating their input, I was able to successfully submit a concept. For a clinical trial for two to be supported by Lilly and in collaboration with, Leading clinical trialists in June ecology and the in the Jioji group,
which is our major cooperative group for research. We actually were able to successfully propose and activate an investigator initiated trial which is GOG 3039, a phase two study of abemaciclib in combination with lectures on advanced recurrent or metastatic endometrioid cancer. This is a phase two single arm trial to evaluate the efficacy of this drug combination for endometrioid and imaginal cancer with dosing based on the current FDA approval for combination therapy and breast cancer. The study endpoints is to evaluate...
the efficacy and in addition, the translational research component, which is all being done here at Yale. We are collecting longitudinally whole whole blood for cell-free DNA as well as FFP of the tissue samples for exploratory analysis and identification of novel biomarkers of response. And how does this trial fit into the rapidly evolving landscape of treatment for endometrial cancer? Well surgery, hysterectomy, removal of the tubes and ovaries, and nodal valuation is still the cornerstone of patients presenting.
with resectable ended mutual cancer.
Following surgery, low end and intermediate risk patients are managed with observation, while high intermediate risk patients standard of care. Some receive radiation therapy or vaginal breakey therapy with the potential benefit of the additional of pembrolizumab for mismatch repair. Deficient patients being evaluated in this trial we have open here, which is the Gio 24 high risk higher risk patients following surgery who are fully respected. Admin therapy includes chemotherapy,
00:52:56.782 --> 00:53:00.066 usually tax on carboplatin.

00:53:00.070 --> 00:53:01.756 With a mentor,

00:53:01.756 --> 00:53:03.442 village individualized radiotherapy,

00:53:03.442 --> 00:53:04.566 often including pelvic radiation,

00:53:04.570 --> 00:53:06.294 if there’s pelvic nodal involvement

00:53:06.294 --> 00:53:08.449 and whether or not pember Lism AB is

00:53:08.450 --> 00:53:11.122 going to offer additional benefit

00:53:11.122 --> 00:53:13.184 to reduce the risk of distant

00:53:13.184 --> 00:53:15.812 Mets in these higher risk women is

00:53:15.812 --> 00:53:18.870 being evaluated in keynote.

00:53:18.870 --> 00:53:20.562 and what about first line therapy

00:53:20.570 --> 00:53:24.426 E 21 for advanced patients measurable disease,

00:53:24.426 --> 00:53:28.140 metastatic disease,

00:53:29.744 --> 00:53:32.150 or recurrent disease?
So the standard of care currently is chemotherapy with GOG 209 showing tax sale, CARBO doublet therapy as to double as adopted from ovarian cancer is seems to be more tolerable than triplet therapy. So that’s become the standard of care and whether or not pember lism AB. Will improve outcomes in these patients who have a very high risk of progression and recurrence is being evaluated in giot, oh. Eighteen also actively enrolling and Guidelines also described hormonal therapy as an option. Would definitely consider Geo G39 for
these patients who would be eligible.

And what about in the second line setting? Currently we have standard of care options for patients who progressed on previous chemo and those include for mismatch repair, deficiency pembrolizumab or just Starla mad. And then for the MMR proficient, we saw that pembrolizumab and inland vatnik combination performed better than physicians choice of second line chemo in the GY and art portfolio. We have a number of biomarker driven therapies being evaluated in a phase two setting,
00:55:01.650 --> 00:55:04.485 and these are led by Doctor Santine,
NOTE Confidence: 0.94380326875
00:55:04.490 --> 00:55:07.070 a fully receptor alpha targeting
NOTE Confidence: 0.94380326875
00:55:07.070 --> 00:55:08.618 antibody drug conjugate,
NOTE Confidence: 0.94380326875
00:55:08.620 --> 00:55:12.652 as well as a trope 2 targeting anti
NOTE Confidence: 0.94380326875
00:55:12.652 --> 00:55:16.062 antibody drug conjugate and certainly
NOTE Confidence: 0.94380326875
00:55:16.062 --> 00:55:18.806 for endometrioid endometrial cancer
NOTE Confidence: 0.94380326875
00:55:18.810 --> 00:55:22.860 would would would recommend consideration
NOTE Confidence: 0.94380326875
00:55:22.860 --> 00:55:26.030 of GOG 39 for these patients.
NOTE Confidence: 0.94380326875
00:55:26.030 --> 00:55:30.930 with up to two prior systemic regimens,
NOTE Confidence: 0.94380326875
00:55:30.930 --> 00:55:34.290 one of which could have been chemo,
NOTE Confidence: 0.94380326875
00:55:34.290 --> 00:55:36.264 one of which could have been immunotherapy.
NOTE Confidence: 0.94380326875
00:55:36.270 --> 00:55:39.420 And we actually have activated over 20
NOTE Confidence: 0.94380326875
00:55:39.420 --> 00:55:43.305 of the 25 selected sites and have
NOTE Confidence: 0.94380326875
00:55:43.305 --> 00:55:48.294 really been having rapid accrual with the.
NOTE Confidence: 0.94380326875
00:55:48.294 --> 00:55:52.600 Current rate of accrual
NOTE Confidence: 0.94380326875
exceeding our expectation of one, and it’s currently one to two patients per week. For this trial, which, if it goes to second stage, would enroll a maximum of 52 patients. I just wanted to briefly touch on that since this is relatively new. Is this NCTM navigator or clinical trial specimen resource and it’s available for validation of hypotheses following already completed exploratory and pilot studies, and this includes a very vast number of specimens.
Including a lot of the specimens that were transferred over from the jioji tissue bank, and there is a workflow available. For exploring what specimens are available and submitting for access to these specimens, for addressing research questions that may require large number of samples that are collected in a very rigorous way and then, how do we fund translational research in the area of some declining support? One of the mechanisms. Which has been super valuable for supporting translational support.
which of course yellow been very successful and has spores and head and neck, lung, and skin cancer. There are very few GYN funded spores, currently only one and ended meet real one in cervical, 5 in ovarian and there’s one new. Sporen that focuses on health disparities and endometrial Varian cancer. So I hope I’ve relate some of my enthusiasm for team science and translational science and conduct of clinical trials for gene cancers, which are relatively rare.
cancers and really way for having exciting and meaningful impact. And I hope I’ve, I hope to yell at people who are interested in collaborating with. Contact me in my emails listed here.

Thank you Gloria. Very interesting, very exciting to see the progress that’s been made and all these trials that are underway. They’re underway, people can please. Type your questions into the chat. While we’re waiting, you might want to talk to Roy Herbst if you haven’t. He’s sort of taking the lead on trying to organize new spores and
NOTE Confidence: 0.935592178333333
00:58:30.801 --> 00:58:32.427 has quite a bit of experience,
NOTE Confidence: 0.935592178333333
00:58:32.430 --> 00:58:33.710 so he might be someone to talk to.
NOTE Confidence: 0.935592178333333
00:58:33.710 --> 00:58:36.006 Be great to have this poor in this
NOTE Confidence: 0.935592178333333
00:58:36.006 --> 00:58:38.362 in this area in the Piola trial.
NOTE Confidence: 0.935592178333333
00:58:38.362 --> 00:58:41.230 It it it was comparing bracket positive.
NOTE Confidence: 0.935592178333333
00:58:41.230 --> 00:58:42.241 Projecting negative patients.
NOTE Confidence: 0.935592178333333
00:58:42.241 --> 00:58:45.110 Was that bracket one or two or or both?
NOTE Confidence: 0.935592178333333
00:58:45.110 --> 00:58:47.020 Did they they stratify that?
NOTE Confidence: 0.850228801
00:58:48.620 --> 00:58:51.662 So in the data that was
NOTE Confidence: 0.850228801
00:58:51.662 --> 00:58:53.690 published in the paper,
NOTE Confidence: 0.850228801
00:58:53.690 --> 00:58:55.916 at least not in the main manuscript.
NOTE Confidence: 0.850228801
00:58:55.920 --> 00:59:00.756 I don’t recall seeing a stratification
NOTE Confidence: 0.850228801
00:59:00.756 --> 00:59:04.830 of the Braca one versus bracket two.
NOTE Confidence: 0.850228801
00:59:04.830 --> 00:59:09.030 They did show the hazard ratios and
NOTE Confidence: 0.850228801
00:59:09.030 --> 00:59:13.717 PFS curves for a few different groups,
and that included the bracket tumor mutation positive.

The braca tumor mutation, positive and HRD positive and then the bracket to mutation. Negative or wild type and HRD positive and then for so. The UM for that trial, the, UM, the benefit was seen in the Braca positive Braca mutated or the HRD positive, which in that trial was determined by the myriad. My choice HRD thing. Uhm and there was not a clinical benefit in the HR proficient Braka wildtype group.
But that’s an interesting question about if there are differences between Bracha one or two. Uhm, mutated, which I’m not sure I’ll look into that though. OK, alright, good. There any other questions from the audience? If not, will thank you Gloria. It was very interesting and also Michaela. I thought we had a terrific series today and we’ll see you all next week, bye. I.