Both in cancer and obviously immunology and response to viruses. And we'll start with our first speaker, doctor lash boost. I allows is, you know, a professor of Medicine at the school of Madison at the US. Having received his medical degree in Budapest and his subsequent
00:00:31.408 --> 00:00:33.853 Doctorate at the University of Oxford blouse is really committed.

00:00:33.853 --> 00:00:36.298 His career to really understanding the biology of breast cancer and leveraging that understanding to fundamentally improving our way to deliver more efficient, more effective, and more successful clinical care.

00:00:38.994 --> 00:00:41.877 You know, through his laboratory work, his work in translation, Medison And frankly, his leadership of clinical trials in clinic research, which have not only investigated new
drugs but also leverage new technologies to better define and predict how women will best respond to therapy.

He really has been the triple thread and actually have academic Medison, and we’re pleased to have him today to share his work in translation and research in breast cancer so loud.

Thank you for Evergreen speak today. Thank you Charlie, for them the opportunity to to give a brief update on some of the translation of projects that we actually have been involved in the past few years here at Yale. Um?

So this is my a disclosure slide and I would like to cover 3 areas.
When is exploiting the emu micro environment of a breast cancer for therapeutic purposes, some potential metabolic vulnerabilities in breast cancer I think exists and I’d like to challenge you to think and you knew very about cancer predisposition or cancer risk category cancer risk. So the road from an idea to a clinical trial or clinical trial result is really very long and often times very sort of tortuous. So as an example, about 10 years ago we published this paper very show at the presence of immune cells in primary tumors, either ER positive or triple negative,
or her two positive breast cancer service.

Let’s outcome in patients receiving order surgery.

Now the treatment and surgery so that people was published in 2010.

I’d like to remind you that in 2010 there is no effective, you know,

there is no effective, you know,

therapy in any disease type.

So we cause this the closing sentence.

This paper was, well,

it remains unknown whether the

Indians selectivity is simply

associated with with a better outcome,

or it’s really the cause of

the battle outcome in disease.
So around the same time in another project with a postdoc in my lab, we also looked at what sort of biological processes or gene expressions, signatures or patterns are associated with the response. Chemotherapy is really a perfect setting where you can correlate a particular biomarker with sensitive to the treatment because you can directly measure the effect of the treatment at the time of the surgery. Patients have no residual.
cancer after the chemo.

They tend to do really well and we call this pathological complete response.

This is again a number of immune signatures. Are Indian related markers fell out so obviously the big question is so is this a mere association or a cause and effect?

Right around that time, in the second half of 2010, the 1st paper came out in the New England Journal of Medicine and eating woman at that have shown that actually manipulating an immune checkpoint,
so we’d illuminate could improve the survival of patients in metastatic melanoma, so that really created an opportunity to test this Kozera fact versus Amir Association. 2012, which is actually the year when I joined the air. We proposed the new Edgemont trial to be an S and ask them would repeal me map. It could improve the pathological complete response rate when combined with chemotherapy. So PMS said, well, now that’s a good idea, but it’s really too toxic and
00:04:20.946 --> 00:04:22.410 it’s way too early.
NOTE Confidence: 0.893426477909088
00:04:22.410 --> 00:04:24.682 So it went to look and proposed them
NOTE Confidence: 0.893426477909088
00:04:24.682 --> 00:04:27.269 the same thing and you ain’t even prior,
NOTE Confidence: 0.893426477909088
00:04:27.270 --> 00:04:28.790 but also for good measure,
NOTE Confidence: 0.893426477909088
00:04:28.790 --> 00:04:30.578 he asked them whether they would
NOTE Confidence: 0.893426477909088
00:04:30.578 --> 00:04:32.140 be interested in Edgmont Prial,
NOTE Confidence: 0.893426477909088
00:04:32.140 --> 00:04:34.114 since since a lot of immune cells
NOTE Confidence: 0.893426477909088
00:04:34.114 --> 00:04:35.346 in the microenvironment predicted
NOTE Confidence: 0.893426477909088
00:04:35.346 --> 00:04:36.996 better outcome of the surgery.
NOTE Confidence: 0.868568539619446
00:04:37.000 --> 00:04:38.925 So for the new regiment they actually
NOTE Confidence: 0.868568539619446
00:04:38.925 --> 00:04:41.127 sent me this lovely letter that I
NOTE Confidence: 0.868568539619446
00:04:41.127 --> 00:04:43.084 thought it’s interesting to read, right?
NOTE Confidence: 0.868568539619446
00:04:43.084 --> 00:04:44.908 So read the actual date first,
NOTE Confidence: 0.868568539619446
00:04:44.910 --> 00:04:46.728 so it’s 18th of September 2012.
NOTE Confidence: 0.868568539619446
00:04:46.730 --> 00:04:47.642 The ordinary nice,
NOTE Confidence: 0.868568539619446
00:04:47.642 --> 00:04:48.858 polite rejection that well,
we are unable to provide either funding or drug for this project because of the unclear. FDA regularly path forward. Either there is well, sort of tried the road for edge event registrations and they agreed to do an agent trial which led to this spoke as 1418 konnakol trial, so not as 40 actually means that it was started in 2014, so it took about two years to the NCI to really put together this large of the randomized registration trial. After Merck supported it in
2012 in principle.
So I’m kind of tenacious and not very aggressive, but I am tenacious.
So I suppose to say my dear again to Med immune in the same year, maybe even at that time was a startup company.
They had do volume app and now they’re smaller than they actually said?
Yeah, why not?
They had do volume app and now they’re part of easiest is Erica and being smaller than they actually said?
Yeah, why not?
So we propose them to studies and they agreed to both.
What was the single agent,
I mean a single arm phase, one phase,
two trial at Yale, and the randomized trial.
So the I spy consortium combined it all, Apple event added to pocket back. So our study at year was just simply. So. Hum. So I could be presented last. There's a historical interest because this was the first knew edgmont even oncology trial anywhere in the world. So the first patient was enrolled in 2015. It was a phase one phase two trial, and because this has never been done in the collective setting.
combined with chemotherapy food,

though,

is chemotherapy before surgery FT

require that the first three patients

is watch for 9 months each week

So it looks like it was a long
time to complete.

The results showed that the
pathological complete eradication
rate in the rest was about 44%.
The same chemotherapy regimen
in a similar trial,
and by the sea by smog.
Southwestern college group resulted
in a PCR or pathological covered
00:06:51.487 --> 00:06:52.907 response with different 29%.

00:06:52.910 --> 00:06:55.016 So we also noted that there,

00:06:55.020 --> 00:06:56.484 as you would expect,

00:06:56.484 --> 00:06:58.680 you cancel each other higher PD

00:06:58.750 --> 00:07:00.772 leg and one expression or more

00:07:00.772 --> 00:07:03.183 sites at a higher PCR eight more

00:07:03.183 --> 00:07:05.358 closer to 60% rather than.

00:07:05.358 --> 00:07:07.140 44 So remember,

00:07:07.140 --> 00:07:10.196 parallel with this and the other study was

00:07:10.196 --> 00:07:12.610 running through the I spy that I was so.

00:07:12.610 --> 00:07:15.730 Lad and he showed the results of the

00:07:15.730 --> 00:07:18.608 Plenary session of the EC are this year on.

00:07:18.610 --> 00:07:20.934 The study shows 9 the randomized setting

00:07:20.934 --> 00:07:23.198 that indeed leave this door vulnerable.

00:07:23.200 --> 00:07:25.015 A product combination improved the

NOTE Confidence: 0.868568539619446
pathological can’t response rate

in both the triple negative group,

which was the results were

very eerily similar in terms

of the PCI rate, 47 versus 44% in

our little negative study at Yale,

and we also notice that

actually this drug also work.

That is combination worked.

It was added to chemotherapy. You have to.

I mean it hormone receptor HR stands

for hormone receptor positive disease.

However, the result might this reason

why this was picked for a plenary

session is actually in the next slide,
so we stumbled upon a remarkably sort of simple and clear way to isolate out among the estrogen receptor positive tumors, the ones which really benefited versus those who did not. There was no editing benefit. So if you split these estrogen receptor hormone receptor positive group into two more likely subtypes, let me call your MP1 and MP2 MP one this crap sort of Mamma print. The lower end of the moment I grew up in the MP two is the Momma Prince Super High score on my printer. Similar sort of predictor that we used
to identify patients who benefit from Edgmont chemotherapy in hormone receptor positive diseases score.

So what we're showing here is that this core itself has a meaning and just being called high risk or benefiting from chemotherapy is valuable, but you actually can also split this look into that really super sensitive to adding. Uh, in Indian checkpoint inhibitor to the chemotherapy.

So in that group, the pathological CR equals 64% versus 22%.

In the chemotherapy alone.

So what is this MP group? So this NP group actually is
the group which has a very high proliferation and the relatively low estrogen receptors signaling, or estrogen receptor sort of activity. Read out that you can capture Biostar generating wearing jeans, and that’s an important sort of piece of information to design the follow-up registration trial for base that we have working with. Because this guy proliferation most regions signaling group is the group that is the least likely to benefit from endocrine therapy. Gotta hand it most likely to
00:09:37.662 --> 00:09:38.266 benefit chemotherapy,
NOTE Confidence: 0.864236354827881
00:09:38.270 --> 00:09:40.424 and we think that this benefit
NOTE Confidence: 0.864236354827881
00:09:40.424 --> 00:09:42.258 could be further augmented by
NOTE Confidence: 0.864236354827881
00:09:42.258 --> 00:09:43.888 by adding indoor follow map.
NOTE Confidence: 0.864236354827881
00:09:43.890 --> 00:09:46.210 So we want to get back to this
NOTE Confidence: 0.864236354827881
00:09:46.210 --> 00:09:48.678 letter in September 2012 from work.
NOTE Confidence: 0.864236354827881
00:09:48.680 --> 00:09:51.067 So a year later, in September 30th,
NOTE Confidence: 0.864236354827881
00:09:51.070 --> 00:09:51.360 2013,
NOTE Confidence: 0.864236354827881
00:09:51.360 --> 00:09:53.390 the FDA approved the first sort of
NOTE Confidence: 0.864236354827881
00:09:53.390 --> 00:09:55.584 drug to be based on pathological
NOTE Confidence: 0.864236354827881
00:09:55.584 --> 00:09:57.906 company response rate in breast cancer,
NOTE Confidence: 0.864236354827881
00:09:57.910 --> 00:09:59.314 and that was purchased.
NOTE Confidence: 0.864236354827881
00:09:59.314 --> 00:10:01.069 So purchasing have improved the
NOTE Confidence: 0.864236354827881
00:10:01.069 --> 00:10:02.448 pathological computer response rate
NOTE Confidence: 0.864236354827881
00:10:02.448 --> 00:10:04.398 in her two positive disease and
NOTE Confidence: 0.864236354827881
00:10:04.398 --> 00:10:06.117 lettered registration of this drug.
So not respecting the idea, and they actually lounge the large randomized trial with a pathological CRS, their endpoint, and to their credit, they invited me back. To the app. Leadership of the trial and the results were actually published this year in the new invention of Madison because it did confirm that indeed, adding parallelism after chemotherapy improves the pathological computer education rate improved the recurrence free survival even after 18 months of median follow up.
So this is the research study that sort of was largely based on these observations. Remember 10 years ago, so it took six. It looks 40 years to actually start this study another six years to complete it, and it would have been completed by now, not for the coded. So it has accrued 923 patients out of 1000 and the results probably will be become available in the next two to three years. So so some cancers that high, you know, you know. Union presence know why so often suffer numbers. Medical student at Yale took on
this project to actually look into the molecular background, or why sometimes have a lot of lymphocytes at this. Last one is now medical country fellow at Sloan Kettering. So we did these families pcaa let me show that many other people did before that triple negative cancer’s had a higher notation count, highly antigen mode and more cytotoxic T cells. However, when you look at the actual group On its own, like triple negative disease or ER
positive cancer, her two positive cancer.

These associations suddenly flip.

This is a correlation matrix.

I don’t expect you to see the numbers, but the colors indicate you the positive correlation when it’s Brown and it’s blue, and the deeper the color, the higher the correlation value. So you can see that the Indian signatures are highly correlated with one another. But on the other hand, is Genomic metrics of generic complexities such as. Mutation load or New Antigen Lord
or deletions or amplifications, loads or comme complexity. We actually are inversely associated with immune Indian presence in triple negative disease and disease, so that was pretty counterintuitive. Counter intuitive in 2017. So when I see things like this, I try to confirm it. So we reached out collaborator and friend Thomas card and ask him to friend Thomas card and ask him to
actually replicate this or with a different methodology and Thomas actually find exact same thing that in primary triple negative disease, the fewer the immune cells they hire. The Genomic heterogeneity and the worst prognosis. So worse. Prognosis means that you have a higher probability for methods. This is so and let us do this hypothesis that maybe the metastatic lesions are actually immune refugees or or escapes. So there are more immune in Earth that Michael Environment is more immune inert and these three brilliant woman took on this project
00:13:18.914 --> 00:13:20.999 or parasitically was a visiting scientist from Hungary or so with.

00:13:20.999 --> 00:13:23.384 Smoking baby that his lab in Charlotte.

00:13:23.384 --> 00:13:26.590 With me and.

00:13:26.590 --> 00:13:30.370 More Gerstein so we rounded up samples which will pair primaries and meds and also a separate Court of primaries.

00:13:30.449 --> 00:13:33.249 and subjected them to a whole series of molecular studies to test it in.

00:13:35.940 --> 00:13:38.299 And that’s not from the same patient, and subjected them to a whole series of molecular studies to test it in.

00:13:38.300 --> 00:13:40.911 and subjected them to a whole series of molecular studies to test it in.

00:13:40.911 --> 00:13:43.018 of molecular studies to test it in.

00:13:44.700 --> 00:13:47.095 so this is just really examples of three sort of simple and straightforward.
findings with teal comes the tumor.

Infiltrating info sites are lower in maximum primary tumors in matched and unmatched chords be dealing.

Expression is the same, it slower.

In in the matter equations and also a whole lot of different Indian signatures are all lower,

consistently showing that there are less Indians and less activity in the breast.

Cancer metastatic micro environment.

Why don’t was really interesting though?

Is that while most of the emu markers went down,

some of the Indian targets actually remain high or or even increased
in the meta static environments.

And these IO targets are potential good set of candidates for offer.

Testing them in the meta static setting, either alone or in combination. Also in combination with established agents.

So we selected the group of this preserved IO targets for a clinical trial that we hope to conduct this support.

Clinical trials it’s called rustic and this is sort of a scheme of it.

And again, this takes this immune targets that we preserved in the meta static setting and testing in the clinic whether
they really have a functional role.

In suppressing the new Micro Hood, so because of lack of time I can’t really talk about all the other Indian projects every day, but I just thought I list them here so we did compare changes in the micro environment before and after therapy and the shouts only published. This give us some ideas what to add to Pembrolizumab Order Volume app to make the treatment even more effective than you actually and setting. Homes we also compared to same day the immune reach, triple negative and the energy or
positive Kansas to see that there is differences in their micro environments and that was done by Paso mirror medical students who is now a resident at the Harvard system the same way. So we did similar comparisons by by race and King blindness. Scientists in my lab is working or not. Of data from a number of different new agent trials that seems to do well. Map kind of what precisely defined predictors, and he rosenblit is Medical College fellow with a very nice people and actually looking at in a large pool
00:16:00.966 --> 00:16:02.876 of data from Foundation Medicine.
NOTE Confidence: 0.843152046203613
00:16:02.880 --> 00:16:04.782 Be like an expression across different
NOTE Confidence: 0.843152046203613
00:16:04.782 --> 00:16:06.859 meta static sites in breast cancer.
NOTE Confidence: 0.843152046203613
00:16:06.860 --> 00:16:09.038 And there are some really substantial
NOTE Confidence: 0.843152046203613
00:16:09.038 --> 00:16:10.904 differences in people like an
NOTE Confidence: 0.843152046203613
00:16:10.904 --> 00:16:12.689 expression depending on what site
NOTE Confidence: 0.843152046203613
00:16:12.689 --> 00:16:14.117 you are actually sampling.
NOTE Confidence: 0.843152046203613
00:16:14.120 --> 00:16:16.728 I’m going to move on to something else
NOTE Confidence: 0.843152046203613
00:16:16.728 --> 00:16:19.206 that really got me excited in the past.
NOTE Confidence: 0.843152046203613
00:16:19.210 --> 00:16:21.436 So if you a few months so.
NOTE Confidence: 0.843152046203613
00:16:21.440 --> 00:16:23.045 Many metabolic processes are catalyzed
NOTE Confidence: 0.843152046203613
00:16:23.045 --> 00:16:25.016 by multiple different isozymes or or
NOTE Confidence: 0.843152046203613
00:16:25.016 --> 00:16:26.300 proteins that really capitalizes.
NOTE Confidence: 0.843152046203613
00:16:26.300 --> 00:16:27.274 Same enzymatic reaction.
NOTE Confidence: 0.843152046203613
00:16:27.272 --> 00:16:29.540 Normal cells usually have many of these,
NOTE Confidence: 0.843152046203613
00:16:29.540 --> 00:16:31.274 and oftentimes in cancer you actually
31
see that one of the isoforms become dominant, so that’s the schema on this figure, right? Normal tissue is both sides. When I sent to our expressed in cancer, I just have one becomes a dominant and the other. one is lost. So we asked how often do we see this in cancer and do this sort of isis and expression changes could harbor. Or or include enzymes that we could target metabolically. March secret visiting scientist faculty from a Polish University to this project on and device. This sort of strategy to look at humanizing forms.
Isozymes managed matched primary tumors in the metastatic lesions

The DC area across 14 different cancer types where this was available than the validated the results in cell lines.

Make sure that this is really observed in the purest system and not just an artifact of difference.

He still different issue compositions and then says the functionality in this depth map data which is basically complete knockdown of all human jeans in about 7 or 8 cell lines and then the conference hits.

We validated in the manual screen.
This is an example for you how this exactly looks.

404 Kansas so this is Csea enzyme.

2 forms ACA&B.

Plots show you that how they still the ACA, which is the red and be which is the blue,

had the expression a normal and an action.

Cancer tissues and you can see that the Blues all go down and cancel.

That means that the expression of this is lost,

of this is lost,

whereas the red remains stable and the red is the sea.

So this thing this is a potentially interesting target.
So when you look at this across different cancer types and indeed app map validation data, then actually what really fell out on the top is this questionnaire carboxylase. Which show this loss of isoenzyme diversity intro different cancer types and was socially but nine different cell lines and each cancer type in the depth map so that map has like several dozens of cell lines for a particular cancer type, like breast cancer. Nine of these showed the same loss of heterozygosity, loss of diversity as we
00:18:50.340 --> 00:18:52.450 saw in the human data.

00:18:52.450 --> 00:18:53.689 Different cancer types.

00:18:53.689 --> 00:18:56.580 And in this case is also validated,

00:18:56.580 --> 00:18:58.771 so most of the cell lines there

00:18:58.771 --> 00:19:00.898 where the CSC was knocked out.

00:19:00.900 --> 00:19:02.886 If it had the dominant expression,

00:19:02.890 --> 00:19:04.318 it really impact viability.

00:19:04.318 --> 00:19:07.125 But the real kicker is that when we

00:19:07.125 --> 00:19:09.197 look up what is known about this,

00:19:09.200 --> 00:19:11.819 it turns out that Pfizer has a drug that

00:19:11.819 --> 00:19:14.314 they put through phase one and phase

00:19:14.314 --> 00:19:16.839 two trials for diabetes and fatty liver,

00:19:16.840 --> 00:19:18.500 and actually showed all the

00:19:18.500 --> 00:19:20.160 metabolic effects that we expected.

00:19:20.160 --> 00:19:21.320 But they discontinued development

NOTE Confidence: 0.857035517692566
last year or two years ago
because of thrombocytopenia, which is wonderful.
Because don’t beside opinion
Because don’t beside opinion
through megakaryocytes really rely
on the normal lipid synthesis,
because from both sides bought off and
every time I turn both sides come off
from the surface supermodel career site,
it takes lipids.
Membranes made it so we answered
the proof that is really works
the way it’s supposed.
So the Anthony to collaboration with
Pfizer to do some additional
preclinical studies and bring
it in the clinic

if it validates so,

we simply throw validation is pre

clinical validation is falling on

the shoulders of Julia fold even

offer Medical College of Fellows and

finish with scientists in my lab.

So before the coveted broke we had a

chance to look at 10 different cell

lines and you see that in the human

sort of achievable concentrations

that you can get in the human serum.

It says a pretty broad inhibitory effect.

And the army is not for coffee.

I could probably show you,
said the combinatorial screen results.

from the high throughputs combinatorial screen that we initially is doing in our core facility at the West campus and also collaborating in jacks to test this drug in PDX models. And we hope to bring this to the clinic. Maybe the year 2.

This is not our paper, it’s the people from nature of it shows the distribution of different sort of mutations in large cities of Kansas. So the striking thing about this
00:20:55.568 --> 00:20:57.986 is that there are these set of
NOTE Confidence: 0.862062811851501
00:20:57.986 --> 00:21:00.020 jeans that affected more than 65
NOTE Confidence: 0.862062811851501
00:21:00.020 --> 00:21:02.300 cases out of close to 3000 Kansas.
NOTE Confidence: 0.862062811851501
00:21:02.300 --> 00:21:04.580 And even in this sort of very modern
NOTE Confidence: 0.862062811851501
00:21:04.580 --> 00:21:06.669 and high sort of accuracy study,
NOTE Confidence: 0.862062811851501
00:21:06.670 --> 00:21:08.225 about 9% of Kansas said
NOTE Confidence: 0.862062811851501
00:21:08.225 --> 00:21:09.158 no driver alterations.
NOTE Confidence: 0.862062811851501
00:21:09.160 --> 00:21:11.344 English challenge you to think about anyway.
NOTE Confidence: 0.862062811851501
00:21:11.350 --> 00:21:14.090 What you think you mean by a driver, Jean.
NOTE Confidence: 0.862062811851501
00:21:14.090 --> 00:21:15.590 So is it a statistical construct
NOTE Confidence: 0.862062811851501
00:21:15.590 --> 00:21:17.245 from any sort of statisticians
NOTE Confidence: 0.862062811851501
00:21:17.245 --> 00:21:18.517 in computational biologist?
NOTE Confidence: 0.862062811851501
00:21:18.520 --> 00:21:20.398 It is actually a statistical construct,
NOTE Confidence: 0.862062811851501
00:21:20.400 --> 00:21:22.672 but of course many of you think about
NOTE Confidence: 0.862062811851501
00:21:22.672 --> 00:21:25.079 this is gene that caused the cancer.
NOTE Confidence: 0.862062811851501
The way I think about this is actually it’s just a narrative tool. So this is actually from the same paper from the supplementary figures, but it shows you the enormous amount of model of Genomic abnormalities of any particular cancer has so retro transpositions, a few dozen number of structural variants, several dozen to several, several 1000. So these are big chunks of the DNA chromosomes missing very larger than the thousands of in Dallas and 10s of thousands of single included variance. Incidentally,
you also see this actually in the CIS, which is a premalignant lesion, so these services, all the.

Well, except it’s not really cancer, but it has the same B 53 mutations clarifications or not.

Just the game keeps you big pools, better weather really.

The function of this these jeans and then the individual jeans is.

So this is a people that many years ago we did nearby Sunday.

She was that he was a medical student.
That year.

Now is a faculty at Sloan Kettering and what I want to illustrate here is that every single cancer which is a column as really a different combination of abnormalities. So if you think about it that way, maybe it’s really the reason. Why cancel the have different layers? Because because of this combinatorial difference that they have. If each of these contributes something then their net effect is really really heterogeneous behavior. But maybe it’s even more interesting. Is this work with DVR? She was.
The students at that time at Yale and now it’s a medical student pad. You sequence all the human kindness ease in 90 two breast cancer, only to see whether there are any. Lowering additional kindness is that it? I guess we didn’t find any, but we really observe though is that there is a very large number of high functional impact. Variance in kindness is bigger germline. I’m still think about for a second, so you actually carry a bunch of germ line so the mutations that inactivator overactive. It kinda seems like PSC kinase or whatnot.
So what does it mean?

So please give us this idea that maybe it’s really. He just focused too narrowly on driver mutations, which are only four of five in a cancel. What actually would be probably also helpful is to look at the context in which this is happening and the constant Israeli hundreds of additional variants that come in from the somatic or the germ line angle. So he proposed this idea that really functional German variance, conkle, jeans and it’s the totality of the functional impact.
High functional impact German variants in cancer Lady Jeans. They could actually determine cancer risk. So we know that there are a few very high penetrance. Cancer is chains like Bronco, but it’s really is the minority women who carry this even very, very strong family history. So what’s accounts for dismissing heredity? You think it’s the totality of very strong family history. So what’s accounts for dismissing heredity? You think it’s the totality of the defects that actually are. Embedded in a whole lot of individually non sort of. Cannot translate that.
And then the next iteration of this, that’s really the combined effect of the germline and somatic events that really lead to the malignant transformation rather than a few individually dramatic effect. And it’s a project that talking is pursuing in my lap towers visiting post doc from. And that is so if it’s really true, then we would expect that woman who developed cancer the younger age will have a lot more sort of deleterious germline events in cancer jeans than people who develop cancer the later age because it’s ultimately the
combined effect of the acquired and the inborn errors that lead to Kansas.

So if you are born with a lot of errors to start with, it’s gonna take a fewer or shorter time to get to reach this critical level. And long, behold, that’s exactly what he observed in a bunch of large series like that ECA or the UK biobank and now just published this paper in Nature Communications. I want to just point out to you because time is short on this very last figure, which is the the comparison, the relationship between the
mutation than in the cancer versus
the variant, the German variant burden by age groups.
So he means younger than 30 and the advocating speak louder than 80.
The installation ship is actually remarkable, patience young who are who have cancer at a younger age and it’s it across all the cancers that letter TCG ahead or the UK biobank. We also get consider the 30s, forties, 50s have a much higher germline variant burden in cancer Lee jeans, and this is like 5 or 6 only jeans then. Then people who get cancer the older age and on the other hand most
fam mos have a much higher mutation
somatic mutation so they can.
So then that led to us
Another idea that So what?
Actually the cancer jeans are in this thing?
That it’s probably a lot broader
sort of repertoire then then
no one Canonical cancel jeans.
no one Canonical cancel jeans.
So you could think that this study?
The Dom Hussein,
who is a PhD student in the
computational biology program and
supervised by Mian Mar Gerstein too.
So how many jeans are actually connected,
one step or two step or three step
away in a pretty important interaction

network from a cancer gene.

So if they are immediately next to it,

then they probably influence

the affective for cancer gene.

If they’re two step removed,

they still probably influence over less,

so there actually a whole lot of jeans, but.

Half of all human jeans are

actually connected.

One or two steps away from

from cancer hub gene.

Most of these are not implicated in cancer,

and if you look at their sort of

functional importance in this gap

database and it turns out that the
further away you get from the cancer hub, the less important they seem to be in survival in the depth map data which supports the idea that there are lot more jeans involved in cancer than what you think you see the same when you look at weather. There is an evolutionary pressure to preserve truncating mutations in these jeans, and again the further away. So the jeans which are one Step 2 step three step away from a concert Hall gene and less and less evolutionary pressure on them four through 4 to exclude truncations.
And it was so carry actually

Somatic mutations. So that’s.

Personalized sort of Jim Langley scored.

That’s sums up all these effects that people are born with cancer chains,

Or young investigator award to pursue together with cow.

And we say this too gruesome pictures out here.

Just remind you guys that this is how airplanes crash.

They actually don’t crash because there is a statistically significant losses of the wings or the engines.
or not every single plane crashes caused by a different combination of individually nonlethal events.
So they fall into groups like human error, which is almost always there, but it’s not the same human error. It’s a different kind of human error. There’s always some kind of a mechanical or instrumental failure, but it’s never the same instrument. So that’s my final slide, really studying the new micro environment. Let us to some some useful ideas about clinical trials are very excited about exploring metabolic
adaptations for therapeutic targets, and we submitted the DOD grant with this with a group of other investigators, and I think I really think that the universe is functionally cancel. Event chains is much larger than we think it is interested in. More stuff at the bottom of the slide shows takes you through the list of publications by our group. So thank you, and this is my lab. Each other. Wow, thank you. That was an impressive array of work on so many fronts. And congratulations on all of it.
I know where we’re a little late on time, so let me just offer up one question. You know? I think you oppose. Obviously a very good case that it’s a combination of germline asmatic events and I’m curious, do you think breast is different? Breast cancer is different than other solid to malignancy’s because obviously germline and semantic events are. Install cancers, but you think breast is somehow different that respect. Yes, it’s different. It’s a matter of fact, so you can group really Kansas even
in this paper that I refer to
be looked at different cancer types,
and this Association starts to fall apart
in Kansas that actually have a very high
environments or customer on exposure, right?
Because that in this sort of
message of this new relationship.
So this relationship is less strong
in lung cancer, bladder cancer,
and some other cancers.
So the real picture of course, is nuance.
It’s much more nuanced.
And the same way.
So the jeans we chat important so the
cancer gene is probably also vary from
some tissue types of tissue type.
So these are the refinements that we are actually working on. Is just that I wanted to give you a repertoire of things that we do, but that’s exactly what we actually addressing in this project right now. Thank you and I know just for time will will move on, but obviously folks can certainly email allow us to.