2 grand rounds.

Virtually yet again.

And we have two speakers today.

So Michael Liebman is an assistant professor of Urology and takes care of the full range of patients with GU cancers.

He graduated from Cornell University and received his medical degree from
00:00:37.137 --> 00:00:39.567 the University of Maryland in Baltimore,
NOTE Confidence: 0.675779826666667
00:00:39.570 --> 00:00:41.830 completing his general surgery and
NOTE Confidence: 0.675779826666667
00:00:41.830 --> 00:00:44.459 urology at Mount Sinai before moving
NOTE Confidence: 0.675779826666667
00:00:44.459 --> 00:00:46.827 on to UCSF where he did it two
NOTE Confidence: 0.675779826666667
00:00:46.827 --> 00:00:48.966 year urologic Oncology fellowship.
NOTE Confidence: 0.675779826666667
00:00:48.966 --> 00:00:53.347 He was recruited to Yale in 2016
NOTE Confidence: 0.675779826666667
00:00:53.347 --> 00:00:56.882 specializing in urologic oncology with
NOTE Confidence: 0.675779826666667
00:00:56.882 --> 00:01:01.320 an appointment at Yale and at the VA.
NOTE Confidence: 0.675779826666667
00:01:01.320 --> 00:01:04.519 His research has largely focused on risk
NOTE Confidence: 0.675779826666667
00:01:04.519 --> 00:01:07.280 stratification and and clinical outcomes,
NOTE Confidence: 0.675779826666667
00:01:07.280 --> 00:01:09.702 and he is widely published and today
NOTE Confidence: 0.675779826666667
00:01:09.702 --> 00:01:12.976 is going to talk to us about Ken new
NOTE Confidence: 0.675779826666667
00:01:12.976 --> 00:01:15.073 risk assessment tools for prostate
NOTE Confidence: 0.675779826666667
00:01:15.073 --> 00:01:17.958 cancer deliver better patient outcomes.
NOTE Confidence: 0.675779826666667
00:01:17.960 --> 00:01:18.682 Michael welcome,
NOTE Confidence: 0.675779826666667
00:01:18.682 --> 00:01:20.126 thank you very much.
Well, thanks so much for the warm introduction and good afternoon, so I'm happy to speak about this question. Can new risk assessment technologies for prostate cancer deliver better outcomes? I have no disclosures, so I'm a urologist whose interest are really focused on urologic cancer, specifically prostate cancer, and this has fueled my interest in understanding how technology is aimed at decision making, are used in men with prostate cancer, a disease with a high burden.
00:01:52.754 --> 00:01:53.906 of decisional conflict.
NOTE Confidence: 0.929726411818182
00:01:53.910 --> 00:01:54.242 Specifically,
NOTE Confidence: 0.929726411818182
00:01:54.242 --> 00:01:55.902 I’m interested in learning how
NOTE Confidence: 0.929726411818182
00:01:55.902 --> 00:01:57.852 they’re being used whether or not
NOTE Confidence: 0.929726411818182
00:01:57.852 --> 00:01:59.287 they’re meeting their intended goal,
NOTE Confidence: 0.929726411818182
00:01:59.290 --> 00:02:01.330 and how they can be optimized.
NOTE Confidence: 0.929726411818182
00:02:01.330 --> 00:02:03.304 So the overarching goal of this
NOTE Confidence: 0.929726411818182
00:02:03.304 --> 00:02:05.564 work is to improve how we screen
NOTE Confidence: 0.929726411818182
00:02:05.564 --> 00:02:07.594 for how we diagnose and how we
NOTE Confidence: 0.929726411818182
00:02:07.662 --> 00:02:09.967 manage early stage prostate cancer.
NOTE Confidence: 0.929726411818182
00:02:09.970 --> 00:02:12.292 So in my time I want to cover the
NOTE Confidence: 0.929726411818182
00:02:12.292 --> 00:02:14.059 rationale for active surveillance,
NOTE Confidence: 0.929726411818182
00:02:14.060 --> 00:02:16.070 the why and how of it,
NOTE Confidence: 0.929726411818182
00:02:16.070 --> 00:02:17.687 and then talk about a series of
NOTE Confidence: 0.929726411818182
00:02:17.687 --> 00:02:19.569 advances in the past decade that have
NOTE Confidence: 0.929726411818182
00:02:19.569 --> 00:02:21.279 been undertaken to help increase the
precision of active surveillance,

focusing on prostate MRI and tissue

cbased gene expression signatures.

And then talk about our work.

Looking at real-world uptake and studies
to estimate the effectiveness of testing.

And lastly,

take a close look at the question

do the equity of the dissemination

of new risk assessment tools.

I want to start with a patient example.

A common scenario that we see in the clinic.

A gentleman referred for an elevated

PSA to 8.1 on routine screening.

He has diabetes,
hypertension, hyperlipidemia.

His father had localized prostate cancer but lived his mid 90s.

He has a prostate biopsy showing three corps police in 3 + 3 or grade Group One prostate cancer and has come to see us for a second opinion.

Based on standard clinical risk stratification, he falls in this green category. The low risk or very low risk criteria. So this patient is presented with a few different options. He can have surgery to remove his prostate, and that’s what that’s what I do. He can have radiation treatment.
00:03:28.210 --> 00:03:30.130 to his prostate or monitoring
00:03:30.194 --> 00:03:32.018 known as active surveillance.
00:03:32.020 --> 00:03:33.651 His inclination is to be monitored and
00:03:33.651 --> 00:03:35.458 not be treated for his prostate cancer.
00:03:35.460 --> 00:03:37.614 He knows people who’ve had treatment
00:03:37.614 --> 00:03:39.690 and didn’t like what he heard.
00:03:39.690 --> 00:03:40.878 So understandably has many
00:03:40.878 --> 00:03:42.066 questions about his options.
00:03:42.070 --> 00:03:43.420 How risky are the treatments?
00:03:43.420 --> 00:03:45.274 How might they affect his quality
00:03:45.274 --> 00:03:46.912 of life and particularly his
00:03:46.912 --> 00:03:48.276 urinary and sexual function?
00:03:48.280 --> 00:03:49.764 And what are the risks if he
00:03:49.764 --> 00:03:50.400 does active surveillance?
00:03:50.400 --> 00:03:51.400 Can the cancer spread?
Our index patient is not alone.

Prostate cancer is the most commonly diagnosed non skin cancer in men,

accounting for nearly 270,000 diagnosis estimated in 2022.

And although the incidence, the ratio of incidents to mortality is heavily skewed,

prostate cancer is still the second leading cause of cancer death in males,

and this finding reflects both the wide heterogeneity of prostate cancer,

with some cancers bearing highly aggressive features,

while others demonstrate an indolent course and may never be capable of...
metastasis or regional progression.

For patients with low risk prostate cancer, such as our patient, we’re fortunate that a vast amount of data has matured. Regarding the safety and long term outcomes of surveillance. And by active surveillance, I’m referring to the careful process of monitoring low risk prostate cancer with the intention of providing curative local treatment in the future. If progression is identified. It is the preferred management for very low risk and low risk prostate.
cancer by the NCCN and in longitudinal studies it is safe with less than 1% risk of mortality within 10 years, and it’s effective at preserving long term quality of life.

The monitoring that we refer to commonly involves periodic PSA monitoring, prostate biopsy and imaging, including prostate MRI. How strong is the data for surveillance in this randomized trial published in 2016 from the UK of nearly 1500 patients randomized to receive surgery, radiotherapy, or active monitoring for low risk prostate cancer,
or the 10 year overall survival is nearly 100% in all groups without significant differences. These striking findings cement the long term safety of surveillance and its centrality in efforts to push back against decades of overtreatment of prostate cancer. As part of this work and as part of this mission, we’ve undertaken formative qualitative interviews to gain insights about the perspectives of patients diagnosed with prostate cancer. We spoke with patients recently diagnosed with low risk prostate cancer.
To get a deeper sense about their experiences. And one patient poignantly told us it was very emotional for me. My first doctor told me that I needed to have surgery or radiation, just very matter of fact. After I heard the word cancer, I didn’t know what to say. I just went blank. And another patient encapsulated it. Quite simply, I wanted to understand the reasons behind why my cancer was low risk or high risk, and why active surveillance could be reasonable for me.
So when faced with a diagnosis that many of us consider indolent, patients frequently feel that their life has been upended and sometimes don’t feel supported by their doctors. In any circumstance, the word cancer evokes very strong and intense emotions and clinicians, including us, are very frequently unaware or unprepared. And most notably, many of our patients want to be well informed about their cancer diagnosis and management to feel agency in their decision making.
and assess their choices from a variety of vantage points. And it's this last point that we really want to focus on today, particularly the emergence of precision diagnostic tools that seek to deliver on the goal of enhanced risk stratification and begin to unpack how their news is delivering on this promise. So although we commonly distill prostate cancer into clinical risk groupings, the disease is in fact quite varied both in terms of its biology and clinical course, and I want to take a few minutes to also explain why A1 size fits
all approach for prostate cancer.

Even low risk prostate cancer may still be too inflexible and not optimally meet the needs of our patients enrolled in active surveillance.

So I showed you earlier at the excellent data from the PROTECT study, which randomized patients to observation, radiation or surgery. In this study, patients did not receive intensive monitoring, but rather we only followed at arms length with PSA monitoring and only had further work up if
they had overt progression.

This is pretty different from how we do things today.

There is no MRI.

There were no men mandated confirmatory biopsies,

and although the overall survival at 10 years was quite good,

there were beginning to see significantly higher risks of local progression and metastatic progression in this group,

likely due to misclassification and therefore this data highlights the extent to which active monitoring must in fact be active.

But just how good are we at
predicting boost disease is going to progress overtime and whose will not our best clinical models based on PSA Gleason score and stage actually performed quite model only modestly with C indices ranging from .52 to 0.7? So we’re really not meeting the mark yet and has significant ground to cover in guiding our patients. The questions that we want to know are actually very practical. For example, how likely is a patient cancer to spread if not treated, how often will monitoring be needed and can treatment be given in time?
Due to a very high prevalence of prostate cancer and its desperate decisional burden, there's perhaps equally important need to present this information coherently to our patients and enable them to make optimal decisions and also live for years with their diagnosis and manage the associated uncertainty.

Several new tests have been developed and are now commercially integrated to improve prognostication for patients with localized prostate cancer considering or enrolled on active surveillance. These tests are all biopsy based.

M RNA expression signatures that
measure genes highly associated with prostate cancer outcomes. The decipher genomic classifier generates a score ranging from zero to 1 from microarray analysis of 22 genes. The uncle Type DX test measures the expression level of 12 genes reflecting androgen signaling cellular organization proliferation and stromal response pathways. And lastly, the Polaris signature is a cell cycle progression score calculated based on the expression levels of 31 genes. Each of these tests yields discrete predictions about cancer risk,
including recommendations

NOTE Confidence: 0.892628519615385

for clinical management.

NOTE Confidence: 0.891811376

So all of these tests are independently

NOTE Confidence: 0.891811376

provide prognostic value compared to the

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standard of care variables such as PSA,

NOTE Confidence: 0.891811376

Gleason, score, and clinical stage.

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The disciple classifier is now the best

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studied and has been validated as both

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a prognostic and predictive marker.

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In one retrospective study where

NOTE Confidence: 0.891811376

the decipher scores were calculated

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based on archival FFP specimens,

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patients in the highest group

NOTE Confidence: 0.891811376

faced substantially greater risk of

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metastatic progression after treatment.

NOTE Confidence: 0.891811376

However, a key point is that each of
these tests have been studied only in retrospective cohorts of patients who have previously been treated, and comparatively little is known about their real-world use or the decisions that arise following testing. The other major advancement has been prostate MRI, something that Yale is truly a leader in. So high resolution prostate MRI affords reliable identification of prostate cancer and facilitates directed or fusion biopsies. It also substantially improves local staging. And it’s now the standard of care in many countries,
including the in the UK,
NOTE Confidence: 0.90124940125
where it’s performed almost
NOTE Confidence: 0.90124940125
universally in patients with known
NOTE Confidence: 0.90124940125
or suspected prostate cancer.
NOTE Confidence: 0.90124940125
And actually, at Yale,
NOTE Confidence: 0.90124940125
in undertaking in the majority of
NOTE Confidence: 0.90124940125
patients in our diagnostic process.
NOTE Confidence: 0.90124940125
In one randomized trial of 500 patients,
NOTE Confidence: 0.90124940125
MRI led to increased detection of
NOTE Confidence: 0.90124940125
clinically significant prostate cancer,
NOTE Confidence: 0.90124940125
and in fact, and actually less
NOTE Confidence: 0.90124940125
detection of low grade cancer.
NOTE Confidence: 0.90124940125
So here’s the breakdown that we can
NOTE Confidence: 0.90124940125
see in this chart over here that
NOTE Confidence: 0.90124940125
the majority of patients who have
NOTE Confidence: 0.90124940125
a high suspicion lesion on MRI are
found to have clinically significant or high grade cancer.
Versus quite low on patients who have a lower suspicion.
So based on improvements in diagnostic accuracy, it’s been assumed that the routine use of prostate MRI will also enhance the use and safety of active surveillance.
So in light of a major shift in the acceptance uptake, there is a pressing need to understand how these two new forms of testing, genomic testing and prostate MRI have impacted its practice.
Use of active surveillance has increased significantly within the past decade. Between 2010 and 2015, data from SEER indicates that the rates have increased from 14.5 percent in 2010 to 42.1% in 2015 among low risk patients. But it’s also worth noting how substantially practice patterns differ for prostate cancer by geography in this elegant study recently published, the authors contrasted changes in active surveillance use, which are these yellow bars on the right by sea region, and so Connecticut. We’re doing quite well, but we really see how market the
differences are between, for example, Connecticut and Greater Georgia. Showing that although changes appear to be continuing, there’s also a really a substantial amount of heterogeneity. So it’s within this context that we aim to evaluate the uptake of risk assessment tools with a particular emphasis on regional considerations, and in this analysis we focus on hospital referral regions, which are Regional Health care markets.
used to characterize variation in the intensity of health care. So we first sought to understand the use of prostate MRI and using Deidentified administrative claims from Blue Cross Blue Shield. We characterize the use of prostate MRI among beneficiaries who have recently diagnosed with prostate cancer. And we found that overall use of prostate cancer increased from 7.2% among patients diagnosed in 2012 to 16.7% in 2018 and 2019. However, it’s clear that the vast variation by region continues to be a
dominant theme in certain areas, such as the Northeast and HRR in Connecticut are high users of Mr. As our parts of the Mid Atlantic where, whereas others show minimal use. And genomic testing presents an interesting distinction because, in contrast to MRI, which has been available for years but only rose in popularity, slowly genomic testing has become approved and reimbursed by payers at roughly all at the same time beginning in 2013 and 2014. Another consideration is that testing is also performed at remote laboratories,
so complex local infrastructure
NOTE Confidence: 0.83584552125

is generally not needed.
NOTE Confidence: 0.83584552125

And these tests are very much
NOTE Confidence: 0.83584552125

discretionary at the discretion
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of the position of the physician.
NOTE Confidence: 0.83584552125

So to answer the question about uptake,
NOTE Confidence: 0.83584552125

we evaluated trends and testing
NOTE Confidence: 0.83584552125

at the HRR level again.
NOTE Confidence: 0.83584552125

In addition to evaluating the
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presence of regional variation,
NOTE Confidence: 0.83584552125

we sought to also understand
NOTE Confidence: 0.83584552125

similarities among regions,
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and we use something called group
NOTE Confidence: 0.83584552125

based trajectory modeling perform of
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finite mixture modeling to identify
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shared phenotypes of adoption.
So to just say it’s simply the big picture goal here is to understand how regional patterns cluster together and help understand what characteristics they might share in common. Using this approach, we uncovered 5 distinct regional clusters of adoption. We can think of these as the rapid adopters red, slow or minimal adopters in the bottom and those that sort of land in the middle. Clusters of regions with the largest expansion of genomic testing had hired median incomes.
and higher education levels, and we did not notably find any significant differences by race.

And these findings are important because they provide the first indication of the extent to which discretionary testing varies geographically and also proposes shared conditions that may be associated with testing. This work also reveals potential gaps in how we are applying.

Testing and get can give us a better sense of the need for consistency in
NOTE Confidence: 0.83584552125
00:16:25.780 --> 00:16:27.350 our guidelines and care practices.
NOTE Confidence: 0.951970950714286
00:16:30.390 --> 00:16:31.900 So understanding that the clinical
NOTE Confidence: 0.951970950714286
00:16:31.900 --> 00:16:33.108 landscape is changing with
NOTE Confidence: 0.951970950714286
00:16:33.108 --> 00:16:34.618 the integration of new tools,
NOTE Confidence: 0.951970950714286
00:16:34.620 --> 00:16:36.654 we also wanted to understand the
NOTE Confidence: 0.951970950714286
00:16:36.654 --> 00:16:38.926 relation of taste testing to actual
NOTE Confidence: 0.951970950714286
00:16:38.926 --> 00:16:41.056 clinical management received by patients.
NOTE Confidence: 0.951970950714286
00:16:41.060 --> 00:16:42.845 But doing this experimentally is
NOTE Confidence: 0.951970950714286
00:16:42.845 --> 00:16:44.630 actually is difficult in observation.
NOTE Confidence: 0.951970950714286
00:16:44.630 --> 00:16:46.766 ULL data, given the absence of
NOTE Confidence: 0.951970950714286
00:16:46.766 --> 00:16:48.190 granular clinical information and
NOTE Confidence: 0.951970950714286
00:16:48.253 --> 00:16:49.869 the absence of randomization,
NOTE Confidence: 0.951970950714286
00:16:49.870 --> 00:16:52.022 a common theme in this work is seeking
NOTE Confidence: 0.951970950714286
00:16:52.022 --> 00:16:54.049 therefore to understand and account for.
NOTE Confidence: 0.951970950714286
00:16:54.050 --> 00:16:56.054 These unmeasured bias is associated with
NOTE Confidence: 0.951970950714286
who gets a test and doesn’t get a test.
And this investigation may be increasingly valuable given the number of auxiliary services in cancer care, including many like MRI and genomics, whose clinical efficacy has not and may never be evaluated in a randomized trial. So we first sought to address this question of the association between prostate MRI use and initial management for prostate cancer. Answer Medicare. After identifying a cohort of patients with low risk prostate cancer by clinical criteria, we examine the association between...
NOTE Confidence: 0.951970950714286
00:17:29.290 --> 00:17:32.291 receipt of a prostate MRI and initial
NOTE Confidence: 0.951970950714286
00:17:32.291 --> 00:17:34.215 observation for prostate cancer.
NOTE Confidence: 0.951970950714286
00:17:34.220 --> 00:17:36.760 And assess the association using
NOTE Confidence: 0.951970950714286
00:17:36.760 --> 00:17:38.284 conventional logistic regression
NOTE Confidence: 0.951970950714286
00:17:38.284 --> 00:17:40.319 and propensity score matching.
NOTE Confidence: 0.951970950714286
00:17:40.320 --> 00:17:44.343 In these analysis,
NOTE Confidence: 0.951970950714286
00:17:44.343 --> 00:17:46.442 we consistently found a strong association
NOTE Confidence: 0.951970950714286
00:17:46.442 --> 00:17:48.809 with an odds ratio of nearly two.
NOTE Confidence: 0.909013288125
00:17:52.050 --> 00:17:55.860 Taking advantage of the substantial
NOTE Confidence: 0.909013288125
00:17:55.919 --> 00:18:00.263 of the substantial regional variation
NOTE Confidence: 0.909013288125
00:18:00.263 --> 00:18:05.360 that we saw in earlier studies,
NOTE Confidence: 0.909013288125
00:18:02.786 --> 00:18:05.360 was also associated with changes in
NOTE Confidence: 0.909013288125
clinical management for prostate cancer.

To do this, we identified over 65,000 patients with prostate cancer and Blue Cross Blue Shield and assess both individual and regional adoption of prostate MRI and genomic testing. And we sought to test the hypothesis that regions with high levels of uptake of MRI and genomic testing had greater changes favoring observation versus treatment for prostate cancer. And what we found was that those eight hours in the highest quartile of adoption of MRI, or associated with a four point 1% increase in observation versus treatment.
and those in the highest quartile. Genomic testing were associated with a 2.5% adjusted increase in observation versus definitive treatment. So the way I think to look at this is that these findings suggest alignment between a regions. Use of a new risk stratification technique occurring at the extremes and changes in observation, ULL management. However, owing to the limitations of this ecological study design, we’re very careful not to directly...
00:19:09.488 --> 00:19:11.380 extrapolate these to patient effects,
NOTE Confidence: 0.909013288125
00:19:11.380 --> 00:19:13.543 but I think the consistency of these
NOTE Confidence: 0.909013288125
00:19:13.543 --> 00:19:14.849 associations and the practical
NOTE Confidence: 0.909013288125
00:19:14.849 --> 00:19:16.769 observation that there seems to be
NOTE Confidence: 0.909013288125
00:19:16.769 --> 00:19:18.781 a certain type or inclination of
NOTE Confidence: 0.909013288125
00:19:18.781 --> 00:19:20.767 institutions or providers who are much
NOTE Confidence: 0.909013288125
00:19:20.767 --> 00:19:22.936 more invested in the idea of surveillance,
NOTE Confidence: 0.909013288125
00:19:22.940 --> 00:19:25.028 suggests that these two may go hand in hand.
NOTE Confidence: 0.9532116
00:19:28.920 --> 00:19:30.992 Another major focus of our work has
NOTE Confidence: 0.9532116
00:19:30.992 --> 00:19:33.090 been to understand the experiences that
NOTE Confidence: 0.9532116
00:19:33.090 --> 00:19:35.010 patients with prostate cancer have.
NOTE Confidence: 0.9532116
00:19:35.010 --> 00:19:37.800 When using these patient facing tools.
NOTE Confidence: 0.9532116
00:19:37.800 --> 00:19:40.155 Through in-depth interviews, we’ve also
NOTE Confidence: 0.9532116
00:19:40.155 --> 00:19:42.510 specifically focused on this point.
NOTE Confidence: 0.9532116
00:19:42.510 --> 00:19:43.645 And would speak and when
NOTE Confidence: 0.9532116
00:19:43.645 --> 00:19:44.326 speaking with patients,
the responses are really quite humbling and often clarifying in their insight. Patients say, often say things like the more data you can get the better, especially if it’s noninvasive, like an MRI or genomic test. But they also expressed uncertainty. I wasn’t really sure about the genetic thing, and we also hear very frank answers about the experiences of going through it. The MRI was loud and I couldn’t breathe. No one told me about it and I wish I knew before. So many patients seem to express this sort of maximalist approach when it comes to
information about their prostate cancer.

However, we also have to realize that in the quest to deliver as much information as possible, we often fall short, especially when it comes to explaining complex predictions. Iterative testing is also not without downsides, as even small low risk procedures can be challenging for patients over the long course of their disease. And lastly, as we make strides in the science and clinical implementation of these tools, it's also vital to ask, are we ensuring that access to testing is equitable?
Or are we perhaps widening gulfs?

This is particularly relevant in prostate cancer, where there are entrenched racial disparities in diagnosis, treatment, and outcome. Black men with prostate cancer in the United States are more likely to be diagnosed with prostate cancer, less likely to receive guideline-concordant care and experience, and have a nearly two-fold greater risk of prostate cancer death. One mechanism through which differences in outcome might occur is less...
access and less use of diagnostic technologies involved in the timely detection of potentially lethal cancers. In our earliest work, we identified substantially lower use of prostate MRI, even adjusting for clinical characteristics among black versus white patients. 38% lower odds of prostate MRI use in patients with low risk prostate cancer and although there are stark disparities, there are also very market differences by region. So, for example, in the Los Angeles City Registry,
15% of patients of black patients with prostate cancer received an MRI versus 28% of white patients.

We do see also disparities in Connecticut. But this is contrasted by some regions where things are relatively equal and Atlanta rates were at approximately 9% for black patients and white patients.

So despite a growing recognition of the existence and pervasiveness of these disparities, little is known about the root causes.

And recently we aim to identify factors that might underlie this disparity in the use of prostate
MRI using a technique known as mediation analysis to breakdown the total effect of a patient race on their likelihood of receiving an MRI. And essentially what we’re trying to do is explain where does this 38% difference come from, and to do this, we proposed a model. Through which the observed disparity may be explained by clinical mediators candidate mediators. In this sort of exist as intervening variables. Those might be explained by clinical factors, socioeconomic status, geography, and structural racism.
Using multiple additive regression trees, a tool of for predictive data mining, we perform mediation analysis to decompose these known disparities into their potential components. Using this approach, we estimated that variation in region accounted for 24% of the observed affective race, 19% to residential segregation, a manifestation of structural racism, 19% to socioeconomic status, and 11% to dual eligibility. A marker for low income or disability. And to our knowledge,
these with the first analysis to propose upstream contributors to inequalities in access to prostate cancer technologies, and we’re hopeful that these results can help inform multi level efforts to improve equitable access and the quality of diagnostic cancer imaging beginning with efforts in our own backyard. So I want to start concluding here by saying that the way that we manage low risk prostate cancer is changing rapidly. One major change that we may see in the future is fewer diagnosis of low risk prostate cancer through the use of refined pre biopsy
decision tools such as prostate MRI and other biomarkers with better specificity for high risk disease. But among patients with prostate cancer, we've also identified gaps in access comprehension and support for patients undergoing complex testing. To close this gap, I think that multifaceted efforts are needed to help improve the consistency and quality of care that we deliver, and this is going to be a clear focus of ours in the years to come. There are also clear opportunities to improve the quality of our predictions.
by leveraging institutional and national data sources such as baseline genomic and imaging characteristics to refine how we predict risk. So I think it’s likely that we’ll look back at these snapshots of gene expression as pretty antiquated relatively soon.

And lastly, I think there’s a great progress in the form of advanced imaging, including pet tracers with high sensitivity and specificity for prostate cancer that will soon likely be part of our diagnosis and tracking. So I want to stop there and conclude.
by saying that new technologies have been deployed to increased precision in the management of low risk prostate cancer patients. When you speak to them clearly value information about their cancer in one agency in the decision making process. Genomic testing and prostate MRI are associated with increased use of observation, but Kohl’s relationship is still not clearly defined. And lastly, as we make strides in the science, we need to sharpen our attention to disparities in access that may in fact
widen racial and geographic disparities.

And I just want to say thank you for your time.

I’m incredibly grateful to my wonderful mentors at the Yale Copper Center, particularly Kerry Gross. Shelmet Mott have been instrumental in developing this work. Extremely grateful to my colleagues in the Department of Neurology and the Yale Cancer Center has also been generous supporters of this work as well.

Thank you. Thanks very much, Michael. If people have questions if they
00:26:00.839 --> 00:26:04.505 can put it in the chat and I’ll
NOTE Confidence: 0.931496585454546
00:26:04.505 --> 00:26:06.985 I’ll ask a question while we’re
NOTE Confidence: 0.931496585454546
00:26:06.985 --> 00:26:09.420 waiting to see what people have.
NOTE Confidence: 0.931496585454546
00:26:09.420 --> 00:26:15.516 So is getting an MRI in it of itself
NOTE Confidence: 0.931496585454546
00:26:15.520 --> 00:26:17.206 something that leads to better care
NOTE Confidence: 0.931496585454546
00:26:17.206 --> 00:26:19.731 or is it a marker of doctors who
NOTE Confidence: 0.931496585454546
00:26:19.731 --> 00:26:21.741 provide a different kind of care?
NOTE Confidence: 0.743726158
00:26:22.750 --> 00:26:24.210 Yeah, it it’s that’s really.
NOTE Confidence: 0.743726158
00:26:24.210 --> 00:26:25.386 I think that the main question
NOTE Confidence: 0.743726158
00:26:25.386 --> 00:26:26.170 we’re wrestling with it.
NOTE Confidence: 0.743726158
00:26:26.170 --> 00:26:28.026 It probably is a little bit of both.
NOTE Confidence: 0.743726158
00:26:28.030 --> 00:26:29.591 I mean, I think that the MRI
NOTE Confidence: 0.743726158
00:26:29.591 --> 00:26:31.193 you know if MRI is not even
NOTE Confidence: 0.743726158
00:26:31.193 --> 00:26:32.780 on the on the table for you,
NOTE Confidence: 0.743726158
00:26:32.780 --> 00:26:34.810 you’re probably receiving one type of care.
NOTE Confidence: 0.743726158
But I think but you know, with these very powerful tools you can, we can make. We can go in the wrong direction very easily because all of a sudden you have. A vast amount of data and one potential concern is that we may overestimate risk because we’re finding you know things that we never found before and then therefore, patients veer off the path of surveillance because you’ve technically have found something that you had to work very hard to look for. Sure, thanks, and there’s a question.
Can you talk a little bit about what we’re doing as an organization to minimize disparities? And I’ll focus specifically on prostate cancer, although it wasn’t written that way. Well, yeah, thank you. I think that you know the first step really is kind of understanding this, and I think that this when we’re so excited about the technology and we’re only beginning to ask these questions. So it starts.
improvement efforts and we have an outstanding quality improvement team within the Department of Urology that’s focused specifically on this question. And so I think that will be part of. Are you know? Interim reporting and quality improvement process to make sure that we are not disproportionately offering these services to certain groups? And and finally, so what’s going on in California and Atlanta that we don’t see the same kind of disparities? Any any clue? I, I think that I mean,
NOTE Confidence: 0.897721886666667
00:28:07.970 --> 00:28:09.870 that you know major centers.
NOTE Confidence: 0.897721886666667
00:28:09.870 --> 00:28:11.424 You know it’s this MRI and
NOTE Confidence: 0.897721886666667
00:28:11.424 --> 00:28:12.460 genomic testing are really
NOTE Confidence: 0.897721886666667
00:28:12.517 --> 00:28:13.889 an early adopter phenomenon.
NOTE Confidence: 0.897721886666667
00:28:13.890 --> 00:28:15.696 So I think we have a
NOTE Confidence: 0.897721886666667
00:28:15.696 --> 00:28:16.298 disproportionate influence.
NOTE Confidence: 0.897721886666667
00:28:16.300 --> 00:28:18.328 I think that in Los Angeles,
NOTE Confidence: 0.897721886666667
00:28:18.330 --> 00:28:20.005 certain medical centers probably also
NOTE Confidence: 0.897721886666667
00:28:20.005 --> 00:28:21.345 have a disproportionate influence,
NOTE Confidence: 0.897721886666667
00:28:21.350 --> 00:28:23.870 so all the more reason to be
NOTE Confidence: 0.897721886666667
00:28:23.870 --> 00:28:25.535 very circumspect and proactive
NOTE Confidence: 0.897721886666667
00:28:25.535 --> 00:28:28.580 in when we roll the when
NOTE Confidence: 0.897721886666667
00:28:28.666 --> 00:28:30.716 we roll these things out.
NOTE Confidence: 0.897721886666667
00:28:30.720 --> 00:28:31.150 Great,
NOTE Confidence: 0.7774961625
00:28:31.890 --> 00:28:33.213 well, I think we’re going to move
NOTE Confidence: 0.7774961625
on to our next speaker, Michael.

NOTE Confidence: 0.7774961625

Thank you very much.

NOTE Confidence: 0.7774961625

It was really great. Thank you.

NOTE Confidence: 0.7774961625

So our next speaker is

NOTE Confidence: 0.7774961625

Carlos Fernandez Fernando,

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who is the Anthony and Brady Professor

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of Comparative medicine and pathology.

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He studied biochemistry and

NOTE Confidence: 0.7774961625

molecular biology at the University,

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Dodge Autonoma of Madrid,

NOTE Confidence: 0.7774961625

and received his PhD at Hospital,

NOTE Confidence: 0.7774961625

Vermont in Madrid as well.

NOTE Confidence: 0.7774961625

He did his postdoctoral work

NOTE Confidence: 0.7774961625

with Doctor William.

NOTE Confidence: 0.7774961625

Tessa here at Yale.

NOTE Confidence: 0.7774961625

His first position was
A faculty position was at NYU, and then he returned to Yale where his research seeks to identify novel mechanisms by which cholesterol and lipoprotein metabolism are regulated and without further comments, I’m going to turn this over to Carlos.

You’re still on mute.

OK, now I see this working well so we can’t see your slides.

OK. Thanks very much.

I really appreciate the invitation for giving the presentation today.

Let me put this in full skin, uhm?
As you mentioned, I’m not a biology or counselor. I did my PhD in biochemistry back in Madrid and at that time I was interested to study how cholesterol metabolism and other lipids regulated leukemia cell proliferation. Since then here I moved to the field of vascular biology for many years until, like about four years ago I got a very incredible, talented student come into my lap. To do that, I do always with the people who has this passion for science,
I ask them whether it is the product they want to do it and then he told me that he was very interested in deep. It’s like he wanted to do something related to two more biology and immunology. And then we came up with this project because has something related to lipids and also it’s a problem related to counter that is is based in the however city or lipid metabolism, Dr. Local phenomena using a mouse. Of the disease. Then I wouldn’t guys like to get full credit to Jonathan, who actually wears the person.
The driving force here. 
Who did this work? Why? 
Why this tumor? 
Why we were interested in a particular carcinoma as this? 
No more, he said he became more prevalent right now, particularly with the situation. 
So overeating and obesity and type 2 diabetes that is, having in all the Western societies. 
Then, as you probably are aware, about 30% of the population in the United States that accumulates large amount of neutral lipids in the
liver and cause this pathology called non-alcoholic fatty liver disease that is quite prevalent from this situation.

We saw that about 25% of the people that has Nathalie our transition to an estate of nasty is non alcoholic. Like that is, which is characterized for the cyclonic inflammation that occurs in the liver and the fibrosis. As well as by the damage and turnover that happened in this particular situation, then this is kind of a chronic disease, but in about 5% of the patients they are able to transition to develop.
This is actually a pretty bad kind of concert, since the survival rate is pretty low in general. Then when we set up the idea for for his thesis, we were actually looking at that time for developing and noble mouse models to start exist and also to apply novel technologies that they start coming out at that time. We try to investigate the molecular level where what could be the driver. So the formation of the catalog in a model of obesity driving tumor formation. Uhm? Around that time, the group from Matthias Eichenwald,
00:33:27.630 --> 00:33:30.290 airing in the Cancer Research Center in Heidelberg, published this novel model of obesity, driving part of local phenomena that was based in feeding the mice without killing. In the upper panel you see a number of papers that this group publishes recently using this. This model of the disease. It’s a pretty good model in our opinion, because, uh, the mice develop all the features that help the people that develop obesity,
type 2 diabetes and ended up having this issue that is increasing body weight,
type 2 diabetes, insulin resistance, and eventually none of them.
But you know, substantial amount of mice develop.
This is one of the benefits of the model that the capital quite well did not have any human disease.
The downside of the model is not not all the mice developed, but of local phenomena only on a small fraction of mice, around 20% of the mice and develop the disease. In 12 months we were unable to reproduce this high.
Incidence of.
In my mind we have to extend our studies to 15 months to see that.
And one of the first thing that we did was to feed the blocks is miles for about 20 months.
With the this calling the fishing Haifa diet and we sacrifice this my son different time points three months and states that is considered to have NFLD.
Six months the NASA state and then we were waiting on the 15 months to study the formation of tumors in mice.
These are in police data from the
the war from Jonathan and and
this is in the upper left corner.
You see the loyal to experiments that
we did here and all the analysis that
we did in every day and in every time
I'm going to show you only a few data about the this the whole study.
But then we actually collect
issues at three six 12115 months
to do lipidomic analysis.
Public functionary sequence
Public functionary sequence
in single sequencing.
Oregon municipal Chemistry not
Oregon municipal Chemistry not
only for delivery but also for
other tissues and also we track
the glucosamine stasis and lipid
00:35:54.144 --> 00:35:55.716 metabolism every time point.

00:35:55.720 --> 00:35:56.760 As you can see here,

00:35:56.760 --> 00:35:58.188 when you start feeling this match

00:35:58.188 --> 00:35:59.529 with Pauline defeating high fat diet,

00:35:59.530 --> 00:36:01.612 this might gain significantly amount of

00:36:01.612 --> 00:36:03.800 body weight and disappears very early on.

00:36:03.800 --> 00:36:05.956 After putting the mice in this diet

00:36:05.960 --> 00:36:09.182 and the increasing body weight is

00:36:09.182 --> 00:36:10.950 accounting because the increasing

00:36:10.950 --> 00:36:14.030 pad mass and the lean mass in

00:36:14.030 --> 00:36:15.956 the masses similar during the

00:36:15.956 --> 00:36:18.532 feeding time but the fat mass is

00:36:18.532 --> 00:36:20.333 significantly increased up on high

00:36:20.333 --> 00:36:22.824 fat diet feeding and these mice in

00:36:22.824 --> 00:36:25.020 in addition to half obesity that

NOTE Confidence: 0.6054106485

65
develop significant dyslipidemia.

Down in the lower panels.

So in the high levels of cholesterol interpolation that are in significant increase in the later time points and this increase in cholesterol correspond to an increase. Circulating levels of LDL lipoproteins and stone in the middle panel. We also perform GTT assets to demonstrate that this mass has insistent and glucose intolerance, and I'll show you here. Also, the fasting glucose in these mice aspects are also significantly elevated.
Then we have a model that developed the three stages of the disease and also recapitulated quite well on the metabolic alteration that is found in people with obesity and anti-two diabetes. Then we also perform Mr. Local analysis in these mice and Carter is well what’s going on. You see the ballooning also there in after three months and six months in high point diet and also a
significant fibrosis and damaging the liver as shown in the right panel by standing with serious right is most developed. 
Fibrosis early on as well, and the formation of fibrosis is also correlated with a significant increase in inflammation. 
So in the analysis and the flow cytometry analysis, or in the lower panel, I’m analyzing the 3:45 positive cells in the liver as well as neutrophils and also monocytes, and Cooper feels as well. Then one other result that we found here. We notice that after 12 months, efficiency of the of the the
people of the development of commercial was quite restricted. We found seven of the 39 mice developed tumors and all of these correlate with the more or less with simulating alpha fetal protein levels in circulation of the mice. As you can see in the in the 15 months group. The incidence of the two more simply significantly many of the money the mice around 50% of the mice develop tumors, and also they feel levels are very hot in the right panels you can see a representative image, so the kind of tumors that you observed.
in this mouse model of the disease.

Then we asked two questions and I'm going to be kind of.

I'm going to summarize all the other we have here, I mean.

Happy to share more when next.

I know you guys it can send us emails we can. We can meet with all of you.

But the two key aspects that you're not gonna want to address here,

you're not gonna want to address here,

we're still first delineated,

the metabolic changes that occurs in a party.

They progress toward the Council.

felt I'm going to show you some. You know fewer slides about that.
And the second part of the talk I'm going to focus a little bit more is about identification or novel. Potential targets that are associated in the development of the disease in this mouse model. Particularly in this protein fatty acid binding protein five that, as I will tell you in a minute, is a protein that is important not only in regulating lipid metabolism. Regulation of the suppression of this protein has been associated not only in liver.
Humans, but also as a highly associated with prostate tumors, as engaging with the first. And part of the first talk of the meeting today. Then if I will be 5 is highly elevated, doesn’t prostate tumors, and there are a number of groups, particularly were collaborators that are looking at selling the efficacy of everything. In treating prostate cancer. Then this is a cartoon. That’s true. The son of the first experiment we did, we took a pentag here the 10 the
the single cell RNA transcriptomics.

Fight change in the pattern of gene expression not only in the patio sites but also in the non parenchymal health, particularly in both illegal sales.

Only minute sales. And then we will turn to look into it. Where are the changes that occurs in the tumor progression and how this has been associated with the disease? Then with the support of the liver center here ideal, we were able to isolate this quite well and you’re not on set up a very good protocol for keep this high.
school Bible on these cells and try to isolate these cells as soon as possible just to avoid any kind of a target effect giving their solution. Then we did the analysis in different stages here and here. You have couple of humor plots. Then here are input.
Five different for different groups. One of them is the mice that are filled with the child diet. Then they might that they were filled with the five fat diet with low AFP expression. Then others would have high FPS present and then we also input directly the DDST carcinoma here. How the diverse populations can be clustered and based in the differential gene expression and different stages from mice that are affecting child.
idea with versus mice that are fed with this calling deficient. Then you see there the path aside and the concepts and cluster and that is in the red box. And as you can see here by the color you can see how the population shifted to the right. Since you had the 1st in normal diet and how they transition to these cancer cells that are highlighted in the purple. These are the purple dots in the path aside group correspond to the cancer cells also within the two more you see. Highly abundant also.
The details suspected that is also in this plot. Then doing this kind of analysis, you can infer all the information coming from all the gene expression for every single event during the transition from the side. The healthy side do the content fell and you can do this kind of analysis called silver time that can tell you how these cells can transition from the healthy to the contact stage. Then this is the nicest. Save the time that you’re not funded and you can see here.
You can actually Coop at this quite well in the trajectories that instills come followed in the cellar time, and can group is also very well in the violent plug in the right panel you can see here probably better where the IPA or the pathways that appears to be deregulated in the process of the converting this healthy, but aside to two more two more cells. One of these boys are now under investigation. I'm going to talk about this. Like binding protein, but also we did metabolic analysis.
here in collaboration with Rachel Berry and follow up very well on these findings but. Things that you can see here is that there is a number of bad ways that appears to be regulated during the transition from the healthy to the malignant L and including the lipid oxidation understand toxic radical and then you have also significant and in regulation of further progress as people lipids, including the importance of transport. Then the molecule I’m going to tell you about today,
fatty acid binding protein actually play an important role in this pathway. So I want to show you why this could be very relevant. One of the question when you do single task to mix now we are trying to do a special transcriptomics to see where I'm located. These cells within the tumor and how. How even is this pressing of the these genes across the tumors? This is decent ongoing war with the collection with sticking one. One of the things that we did in parallel in another different study that the Inmaculada Root Maldonado
help help in this this world is trying to develop another mouse model here that is a rainbow. Mice that allow you to study more clonality this mouse model that thing that does is randomly labeled the patio sites in three different colors. As you can see in the center pictures. These are the control mice and then you can see here where is the random distribution of all the paper cites in the three different colors and in green color are stain and the cells that are non epicycles. This correspond to the endothelial cells.
And the mother was quite well to study.

Regeneration is something I'm not going to touch today, but here in the right panel you see in a model of liver injury that treatment with carbon tetrachloride that induce death. And then you can start regeneration. You can see how you see a very nice clonal expansion of some of the existing apotheosized to develop these patches in different colors.

Then we also employ in this same model to see where we actually happen in the context of aging and the context and situation where we have a chronic metabolic damage.
What's happened with naphthalene, and this is actually very interesting, as you can see here, because even in US you see their selection on some specific clones that occurs in the liver in the left panel, and this is probably because you have this damage and regeneration. Delivery is a very interesting organ to study that. And you can see also accumulation of fat here with showing this like dark spot. But why I want to illustrate you this model and why it's very interesting. This model is because you can.
00:47:19.064 --> 00:47:20.200 actually start to mortality.
NOTE Confidence: 0.667202877047619
00:47:20.200 --> 00:47:22.420 Then you can not only see.
NOTE Confidence: 0.667202877047619
00:47:22.420 --> 00:47:24.076 Diversity of two more sales by
NOTE Confidence: 0.667202877047619
00:47:24.076 --> 00:47:25.760 single seller and just get to me.
NOTE Confidence: 0.667202877047619
00:47:25.760 --> 00:47:27.725 But you can actually interrogate
NOTE Confidence: 0.667202877047619
00:47:27.725 --> 00:47:29.794 whether the two more unit for one
NOTE Confidence: 0.667202877047619
00:47:29.794 --> 00:47:32.000 cell that expanding a single clone of
NOTE Confidence: 0.667202877047619
00:47:32.000 --> 00:47:34.058 is coming from two different clones.
NOTE Confidence: 0.667202877047619
00:47:34.060 --> 00:47:36.204 And the thing that we are seeing now
NOTE Confidence: 0.667202877047619
00:47:36.204 --> 00:47:38.260 is preliminary is that many of these
NOTE Confidence: 0.667202877047619
00:47:38.260 --> 00:47:39.780 two more oligoclonal or monoclonal.
NOTE Confidence: 0.667202877047619
00:47:39.780 --> 00:47:41.656 This is the right you can see
NOTE Confidence: 0.667202877047619
00:47:41.656 --> 00:47:43.677 only two cells or maybe 2 patches
NOTE Confidence: 0.667202877047619
00:47:43.677 --> 00:47:45.399 and only in blue and yellow,
NOTE Confidence: 0.667202877047619
00:47:45.400 --> 00:47:48.298 suggesting that some of this too much
NOTE Confidence: 0.667202877047619
00:47:48.298 --> 00:47:50.498 pressure originated one or two cells.
Doug knows the kissing status and started providing status started. The United two more so in there. And we’re using these kind of tools to map. The molecular mechanism how? How diet induce? Obviously this is actually a very nice model. Also to study metastasis. The model can do it. You can actually track all this Cape and track those cells in different colors to see where the mass is being caused by the tumor’s oriented in blue color or unity in jello color. And then this can be a stand and be.
using for other kind of tumors as well.

Then one other thing that we're trying to look here is OK where you know this could be important. That may drive this, and this is when we identify 55 then then in the left panel. This is uhm again. So in the suppression of alpha fetal protein and this is a totally restricted in most of all the content cells that is not actually expressed in this adult in the adult hepatocytes. Then if I will be 5, it's identified here as a very. You know remarkable and very specific
00:49:01.414 --> 00:49:03.741 for this tumour cells and and you can
00:49:03.741 --> 00:49:05.660 actually interpret this in the cellar time,
00:49:05.660 --> 00:49:07.028 if I will be 5 here.
00:49:07.030 --> 00:49:08.997 When you import the seller time and
00:49:08.997 --> 00:49:11.251 put here the events in different colors
00:49:11.251 --> 00:49:13.760 again in these dots corresponds to
00:49:13.760 --> 00:49:17.240 the patricide in different diets and
00:49:17.240 --> 00:49:20.299 coming from from different animals with low,
00:49:20.300 --> 00:49:23.135 high or directly from the Patella carcinoma.
00:49:23.140 --> 00:49:25.165 And you can see here that the
00:49:25.165 --> 00:49:27.475 expression of every five in healthy
00:49:27.475 --> 00:49:29.968 liver is pretty much nothing over.
00:49:29.970 --> 00:49:30.741 Very lowest price,
00:49:30.741 --> 00:49:32.909 but then they start to be highly suppressed
00:49:32.909 --> 00:49:34.811 when when the match start developing
tumors which is actually there came out.

Very interesting for us because if you want to target something or silence something, it's better to silence something in the liver that is not expressing a healthy tissue.

Then you should expect a very low or non off target effect or the therapeutical intervention.

That is something is by expressing the liver and maybe you are messing around with another different function that could be important for other things.

And this is why it was very interesting for us to follow at this target.
here and try to identify also buy monistat demonstrate expression of animals committee analysis so in very clearly here in the green color. The highest president of 85 and again highly restricted to 2 more when you compare with a healthy agent. Healthy liver in the in the lower in the lower panel and again this. It’s pretty much whistle, so corroborated by Western blot analysis in the right place. As I mentioned to you, and this was very exciting and now
when you go to the human teeth that you can see that but you know not only my mentioned before so caustic content. Has high levels. I think that’s enough and not only is very elevated, but also the overall survival of the persons with phenomenal at fast, high levels of advice significantly diminished with those that have low expression.

Then well, what is 55 doing and then when you start to see the territory? I’m not only in the context of the cancer, feel like another field, you see that you know we have as
many scenes and it’s not clear still

is the mechanism of action that can

have passed in the tumor pressing.

Then I tell you be 5 and the renal name

was given like SVP 5 because it’s highly

is highly

expressed. Their win was was found.

Uhm, has been associated with multiple

has been associated with multiple

tumors, as I mentioned to you.

Long trusted and then the mechanism faction

that has been ascribed or if it be 5 is,

there are several one of them that

there probably is the most established

is that the F B5 is a little chop

around that binds to this party.
Particularly by Mary got it appears to be a very potent Liam for that and activate the people better then and then regulate fatty acid synthesis and storage, but also regulates a lot preparation as well.

There were also a number of other papers, particularly in San Fran, and it appears that they studied the role of T cells die actually discovered at 55 is actually a mitochondrial protein. There that maybe the transfer of fatty acids and it’s important for the Christian morphology in the mitochondrion, also controlling the fatty oxidation. Please dance as well.

And also there were a number of
other papers out there.

Point out that 55 can control actually ER and maybe content and therefore control translation control.

Also the activation of standard transcription factor that resides in the ER and also may regulate as well.

The ER stress in these cells.

Then we have generated the conditional local mass model that now are on the diet we we don’t know. We’re looking forward for the genetic model, but in the meantime we call out my Martin Passando Gemma who got a
multimillion ground with a group in Cold Spring Harbor to use the fighting hitters for treating prostate contact. Main character is so nice in the left the doctor organized the chair. Of that chemistry and they developed those specific incubators for 75. Then we call them Adam, basing the size. Large amount of this indicator for us for treating the HTC in this model. Then the thing that we did here is treating blacks eat mice with the high fat diet calling defeating diet for 12 months, then inject the inhibitor and then track the two more progression for the
next demo and evaluate also potential tumor.

And this is a data that was really incredible

for us because the data was stunning.

we were not expecting such

as a nice outcome in this model.

The thing that you see here is that

when you leave the mice to progress

without treating or vehicle treated,

you see that again we were able to

reproduce the data we saw previously.

That about 50% of the mice developed tumors.

But when you treat these mice.

For the last three months and keeping

the mice and I do see that the two more
00:54:29.850 --> 00:54:31.690 incidents in significantly reviews
NOTE Confidence: 0.545212474428572
00:54:31.690 --> 00:54:34.726 which we only observe only 6 of 20.
NOTE Confidence: 0.545212474428572
00:54:34.730 --> 00:54:35.555 Did not work.
NOTE Confidence: 0.545212474428572
00:54:35.555 --> 00:54:37.480 Even more remarkable is when we actually
NOTE Confidence: 0.545212474428572
00:54:37.531 --> 00:54:39.667 measure that replating anything this nice.
NOTE Confidence: 0.545212474428572
00:54:39.670 --> 00:54:40.114 Yeah,
NOTE Confidence: 0.545212474428572
00:54:40.114 --> 00:54:41.890 you can see that.
NOTE Confidence: 0.545212474428572
00:54:41.890 --> 00:54:45.422 There you see levels increase in the
NOTE Confidence: 0.545212474428572
00:54:45.422 --> 00:54:47.366 mice that progress towards the disease,
NOTE Confidence: 0.545212474428572
00:54:47.370 --> 00:54:50.610 but those miles adapted with the.
NOTE Confidence: 0.545212474428572
00:54:50.610 --> 00:54:54.306 Incubator not only you stop the progression,
NOTE Confidence: 0.545212474428572
00:54:54.306 --> 00:54:56.308 but you see also a regulation of
NOTE Confidence: 0.545212474428572
00:54:56.308 --> 00:54:56.850 these bodies.
NOTE Confidence: 0.545212474428572
00:54:56.850 --> 00:54:59.866 Then this telling us that this
NOTE Confidence: 0.545212474428572
00:54:59.866 --> 00:55:02.746 track price not only preventing
NOTE Confidence: 0.545212474428572
00:55:02.750 --> 00:55:05.870 but it’s only private private from
something that we had to study.

We had to do further studies with imaging and use my miles to make this as a conclusion.

Then you Nathan did a number of studies here, and this summarizing 3 or 4 slides.

But this is the pathway analysis that he did in this tumor cells.

This is coming also from the single cell RNA transcriptomics as well.

Then this is actually restricted to the other side within the phenomena.

But things that you can see again is.

You see also that the suppression of these five you see an increase in pressure.
Someone living metabolism Bedok
sedation things that you sit down in the model you start to see higher here.
Uhm? He's also a number of. And all that analysis in in human cells.
Then this is the the study that he did in age who is 7 human local cinema line.
And try to go even induce you know deeper study here where he treat with inhibitor.
These tales for 48 hours and they are not sequencing analysis and again.
He found many pathways that it was being out there and one of them that was remarkable clear is that they are stress and I'm going to show you some data regarding that thing appears.
to be significantly up regulated
in my city with the typing.
Then for the Penguin analysis, the data.
These data suggest that this incubator influence or regulate the pool of industrial chain fatty acids.
We are now doing a bit American allocates and those tumors and also proving that at the biochemical level and free radical accumulation.
Jonathan follow up is I’m going to show you another,
but he has also data in these cells,
proving that at the biochemical level and also so very clear data showing
00:57:07.224 --> 00:57:08.792 that the oxidative stress also in
NOTE Confidence: 0.797661448
00:57:08.792 --> 00:57:10.316 the US here stressing these tales.
NOTE Confidence: 0.797661448
00:57:10.320 --> 00:57:10.745 Unluckily,
NOTE Confidence: 0.797661448
00:57:10.745 --> 00:57:13.720 this induced cell death in this match.
NOTE Confidence: 0.797661448
00:57:13.720 --> 00:57:16.254 In there in these two more cells.
NOTE Confidence: 0.797661448
00:57:16.260 --> 00:57:19.100 This is the heat map from scientist pathways.
NOTE Confidence: 0.797661448
00:57:19.100 --> 00:57:22.592 You can see that the pair UTR padway being
NOTE Confidence: 0.797661448
00:57:22.592 --> 00:57:24.831 significantly unregulated in the mice.
NOTE Confidence: 0.797661448
00:57:24.831 --> 00:57:26.180 And just to finish,
NOTE Confidence: 0.797661448
00:57:26.180 --> 00:57:28.782 because I'm running out of time, yes,
NOTE Confidence: 0.797661448
00:57:28.782 --> 00:57:32.226 the last couple of slides this is.
NOTE Confidence: 0.797661448
00:57:32.230 --> 00:57:34.414 An example of some of the experiments
NOTE Confidence: 0.797661448
00:57:34.414 --> 00:57:35.350 he did here,
NOTE Confidence: 0.797661448
00:57:35.350 --> 00:57:38.972 and when we did with the cells and she
NOTE Confidence: 0.797661448
00:57:38.972 --> 00:57:41.450 very nicely over with very bad way.
NOTE Confidence: 0.797661448
00:57:41.450 --> 00:57:42.614 And not only that,
but when he did also understanding here and also an accident to track.

I felt better so that their treatment with the SP FY103 in DSL data higher dose. Obviously, one thing that we’re really must looking for ways to the data with the genetic model that we’re developing right now, we know that this inhibitor, despite you know they show a high efficacy and how specificity can have some after that fact, and we’re trying to combine this with the genomic data just to demonstrate the role.
Sucky role of fighting into more pressing then this is a little bit the summary of this of this work I’m doing so many things, Trump carries that the suppression of.

Mr accumulation of fatty acid.

Resulting in increasing years, just new Paris Ponce leading to Apple classes.

This is only like 50% on the part of the cancer cell metabolism reducing this year stress and
and dependent apoptosis in in.

Directly related to other side, but also he found a very interesting wire in the two Micron violent.

In these tumors.

One thing that was very clear for the single. Analysis is that that would be 5 positive.

Macrophage has more kind of and inflammatory terms and then when you actually suppress this you leave more.

The formation of 19 presentation failed, that they stimulate more T cells and this.

Activation have working activity on these two more cells and then we we think that this inhibitor,
which is actually very interesting,

is working in different ways,

not only reacting in the counterfoils.

But those show acting at the in the two

more microenvironment at the level of the

immune response within the two months.

Jonathan served all the credit for this work.

He took the challenge to do it and.

Did many models to study this

and employing novel technology.

then then he really did the the

person who decided credit for this

work and also my laboratory has
I have been actively collaborating all the time with the laboratory Suarez. I would like to thank so Steven and you Meow who are helping us with the Murphy's technology to map out the special task atomic level with this happening in these tumors. Also Rachel Berry City than unbelievable work. Stop trying to show that I'm doing the metabolic analysis that happen within these tumors with this pinned analysis that is doing in her lab. Is fantastic collaboration and also marketing Stony Brook for providing
not only inhibitor but also the FTP
Firefox miles that they developed
in the laboratory and with this
habit technique question.
So
thank you very much, Carlos.
We're a little short on time,
but there are a couple of questions
in and why don’t we get to those?
So the first is based on your mouse model.
Do you have any explanation why
Nash related liver cancer is less responsive to tyrosine kinase
inhibitors or immunotherapy?
Then viral related patterns
cited against her.
Well, I think it's a great question and I think we will take note of that because I didn't know. But the thing that we see is a very strong component in the muni response in these tumors with high fat diet, we don't think that they discuss actually with Jonathan is to look into the other data from Michael, Karen and others that use models of cathedrals in induced coma and just to compare, where are the immune landscape in these tumors compared with the high fidelity user?
Then, and this is a great question, then about the map kinase we got. We got a pilot grants here at the L and we partner with Anthony Bennett who actually work in mechanics and then we are looking in this pilot for the transition between novelty and mass, but the part of the things that they are going to study is with issues that we have in this nice. We’re going to look how all these mechanics activity is being affected during the transition of friendliness and potentially in the cinema, but both both are great questions and we are looking into that.
And in that question was from her to Chow, and this is from Claire Flannery great talk. Thank you. We’re experiments for HTC development done in female mice. If so, were there any difference in HTC development time relative to male mice? Well, great question also and I think it’s a great question because you know today that the user not granted NIH. Then I want to point out that we did this experiment with with money it was not supported by grants. And obviously I mean you can.
You can analyze the standard.

The study takes two years, but I'm going to be short in the answer.

We need only in males, but will be extremely interesting to do in females then.

Then we did some experiments in female there.

Rainbow studies were done in females.

and the two more incidents actually in females are significantly lower than males.

OK, then you have to wait even like two years in high fat diet and the tumor extent is not the thing that you see in then.

It's difference in male and females.

This has been shown this in modern cinema.

In mice I I know, I know,
01:03:36.660 --> 01:03:38.375 much aware about the literature in human,
NOTE Confidence: 0.786601756428571
01:03:38.380 --> 01:03:40.900 I should be more aware now after I
NOTE Confidence: 0.786601756428571
01:03:40.900 --> 01:03:43.252 sent him again, I will read more,
NOTE Confidence: 0.786601756428571
01:03:43.252 --> 01:03:46.750 but but at least in mouse models OK?
NOTE Confidence: 0.786601756428571
01:03:46.750 --> 01:03:50.224 Because being shown that in in the in
NOTE Confidence: 0.786601756428571
01:03:50.224 --> 01:03:53.471 other models the females asked happen
NOTE Confidence: 0.786601756428571
01:03:53.471 --> 01:03:56.727 here develop significantly as less tumors,
NOTE Confidence: 0.786601756428571
01:03:56.727 --> 01:04:00.066 and this has been associated in part
NOTE Confidence: 0.786601756428571
01:04:00.070 --> 01:04:02.968 to the adipose tissue production of
NOTE Confidence: 0.786601756428571
01:04:02.968 --> 01:04:05.450 adiponectin and another or modes.
NOTE Confidence: 0.786601756428571
01:04:05.450 --> 01:04:07.226 Then it’s not clear whether this
NOTE Confidence: 0.786601756428571
01:04:07.226 --> 01:04:08.410 is translated to human,
NOTE Confidence: 0.786601756428571
01:04:08.410 --> 01:04:10.601 but looks at all the depots that
NOTE Confidence: 0.786601756428571
01:04:10.601 --> 01:04:12.645 are different fat depots that are
NOTE Confidence: 0.786601756428571
01:04:12.645 --> 01:04:14.761 different in male and female appears
NOTE Confidence: 0.786601756428571
to be affecting the hormone secretion.

It has an impact on the tumor formation, at least in mice.

Then then it’s a great question we should do.

We have the rainbow Maes was done in females and This is why I tell you that in this model the two more incidences is less, but yes, I mean we should actually try to do them more,

Well, there are other questions, but I think we’re gonna have to end because it’s five after one.

You guys can send me by my email.

Yeah, thank you. Yeah
thanks thanks so much thanks.

Thanks to thank you Carlos.

And thanks to both of our speakers.

See you all next week.