00:00:00.000 --> 00:00:02.823 2 grand rounds.

00:00:02.823 --> 00:00:05.646 Virtually yet again.

00:00:05.650 --> 00:00:10.300 And we have two speakers today.

00:00:10.300 --> 00:00:12.288 Doctor Michael Lippman and

00:00:12.288 --> 00:00:13.779 Doctor Carlos Fernandez,

00:00:13.780 --> 00:00:15.652 Hernando and Doctor Leibman,

00:00:15.652 --> 00:00:18.856 is gonna be first and let me

00:00:18.856 --> 00:00:22.010 just briefly introduce him.

00:00:22.010 --> 00:00:25.370 So Michael Liebman is an assistant

00:00:25.370 --> 00:00:28.994 professor of Urology and takes care of

00:00:28.994 --> 00:00:32.700 the full range of patients with Gu cancers.

00:00:32.700 --> 00:00:34.675 He graduated from Cornell University

00:00:34.675 --> 00:00:37.137 and received his medical degree from

00:00:37.137 --> 00:00:40.319
the University of Maryland in Baltimore,
completing his general surgery and urology at Mount Sinai before moving on to UCSF where he did it two year urologic Oncology fellowship.
He was recruited to Yale in 2016 specializing in urologic oncology with an appointment at Yale and at the VA. His research has largely focused on risk stratification and and clinical outcomes, and he is widely published and today going to talk to us about Ken new risk assessment tools for prostate cancer deliver better patient outcomes. Michael welcome, thank you very much.
00:01:20.630 --> 00:01:22.905 Well, thanks so much for the warm introduction and good afternoon,

00:01:22.905 --> 00:01:24.530 so I’m happy to speak about this question.

00:01:24.530 --> 00:01:30.490 Can new risk assessment technologies for prostate cancer deliver better outcomes?

00:01:30.490 --> 00:01:33.990 I have no disclosures, so I’m a urologist whose interest,

00:01:33.990 --> 00:01:36.358 as mentioned, are really focused on urologic cancer,

00:01:36.360 --> 00:01:39.078 specifically prostate cancer,

00:01:39.080 --> 00:01:44.937 and this has fueled my interest in understanding how technology is aimed at decision making,

00:01:44.937 --> 00:01:46.480 are used in men with prostate cancer, a disease with a high burden

00:01:46.480 --> 00:01:48.390 is aimed at decision making,

00:01:48.390 --> 00:01:50.448 are used in men with prostate cancer,

00:01:50.450 --> 00:01:52.754 as mentioned,
00:01:52.754 --> 00:01:53.906 of decisional conflict.
00:01:53.910 --> 00:01:54.242 Specifically,
00:01:54.242 --> 00:01:55.902 I’m interested in learning how
00:01:55.902 --> 00:01:57.852 they’re being used whether or not
00:01:57.852 --> 00:01:59.287 they’re meeting their intended goal,
00:01:59.290 --> 00:02:01.330 and how they can be optimized.
00:02:01.330 --> 00:02:03.304 So the overarching goal of this
00:02:03.304 --> 00:02:05.564 work is to improve how we screen
00:02:05.564 --> 00:02:07.594 for how we diagnose and how we
00:02:07.662 --> 00:02:14.059 manage early stage prostate cancer.
00:02:12.292 --> 00:02:12.292 So in my time I want to cover the
00:02:14.060 --> 00:02:14.059 rationale for active surveillance,
00:02:14.059 --> 00:02:16.070 the why and how of it,
00:02:16.070 --> 00:02:17.687 and then talk about a series of
00:02:17.687 --> 00:02:19.569 advances in the past decade that have
00:02:19.569 --> 00:02:21.279 been undertaken to help increase the
NOTE Confidence: 0.929726411818182
00:02:21.328 --> 00:02:22.948 precision of active surveillance,
NOTE Confidence: 0.929726411818182
00:02:22.950 --> 00:02:26.208 focusing on prostate MRI and tissue
NOTE Confidence: 0.929726411818182
00:02:26.208 --> 00:02:28.380 based gene expression signatures.
NOTE Confidence: 0.929726411818182
00:02:28.380 --> 00:02:30.096 And then talk about our work.
NOTE Confidence: 0.929726411818182
00:02:30.100 --> 00:02:32.554 Looking at real-world uptake and studies
NOTE Confidence: 0.929726411818182
00:02:32.554 --> 00:02:34.900 to estimate the effectiveness of testing.
NOTE Confidence: 0.929726411818182
00:02:34.900 --> 00:02:35.578 And lastly,
NOTE Confidence: 0.929726411818182
00:02:35.578 --> 00:02:37.951 take a close look at the question
NOTE Confidence: 0.929726411818182
00:02:37.951 --> 00:02:40.521 of the equity of the dissemination
NOTE Confidence: 0.929726411818182
00:02:40.521 --> 00:02:42.676 of new risk assessment tools.
NOTE Confidence: 0.929726411818182
00:02:42.680 --> 00:02:45.024 I want to start with a patient example.
NOTE Confidence: 0.929726411818182
00:02:45.030 --> 00:02:47.046 A common scenario that we see in the clinic.
NOTE Confidence: 0.929726411818182
00:02:47.050 --> 00:02:49.510 A gentleman referred for an elevated
NOTE Confidence: 0.929726411818182
00:02:49.510 --> 00:02:52.170 PSA to 8.1 on routine screening.
NOTE Confidence: 0.929726411818182
00:02:52.170 --> 00:02:53.550 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.

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
to his prostate or monitoring known as active surveillance. His inclination is to be monitored and not be treated for his prostate cancer. He knows people who’ve had treatment and didn’t like what he heard. So understandably has many questions about his options. How risky are the treatments? How might they affect his quality of life and particularly his urinary and sexual function? And what are the risks if he does active surveillance? 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
00:04:24.987 --> 00:04:26.775 metastasis or regional progression.

00:04:29.170 --> 00:04:31.704 For patients with low risk prostate cancer,

00:04:31.710 --> 00:04:32.790 such as our patient,

00:04:32.790 --> 00:04:34.140 we’re fortunate that a vast

00:04:34.140 --> 00:04:35.450 amount of data has matured.

00:04:35.450 --> 00:04:37.840 Regarding the safety and long

00:04:37.840 --> 00:04:39.752 term outcomes of surveillance.

00:04:39.760 --> 00:04:41.148 And by active surveillance,

00:04:41.148 --> 00:04:43.230 I’m referring to the careful process

00:04:43.289 --> 00:04:44.914 of monitoring low risk prostate

00:04:44.914 --> 00:04:46.980 cancer with the intention of providing

00:04:46.980 --> 00:04:49.260 curative local treatment in the future.

00:04:49.260 --> 00:04:51.900 If progression is identified.

00:04:51.900 --> 00:04:53.952 It is the preferred management for

00:04:53.952 --> 00:04:56.404 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,
00:05:31.880 --> 00:05:33.704 or the 10 year overall survival
00:05:33.704 --> 00:05:36.420 is nearly 100% in all groups
00:05:36.420 --> 00:05:38.220 without significant differences.
00:05:38.220 --> 00:05:40.055 These striking findings cement the
00:05:40.055 --> 00:05:41.890 long term safety of surveillance
00:05:41.950 --> 00:05:43.540 and its centrality in efforts
00:05:43.540 --> 00:05:45.580 to push back against decades of
00:05:45.580 --> 00:05:47.156 overtreatment of prostate cancer.
00:05:49.350 --> 00:05:50.742 As part of this work and as part
00:05:50.742 --> 00:05:52.320 of this mission, we've undertaken
00:05:52.320 --> 00:05:53.980 formative qualitative interviews to
00:05:53.980 --> 00:05:56.573 gain insights about the perspectives of
00:05:56.573 --> 00:05:58.758 patients diagnosed with prostate cancer.
00:05:58.760 --> 00:06:00.200 We spoke with patients recently
00:06:00.200 --> 00:06:02.000 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
00:08:29.252 --> 00:08:31.180 predicting boost disease is going to
NOTE Confidence: 0.931398748181818
00:08:31.180 --> 00:08:33.136 progress overtime and whose will not
NOTE Confidence: 0.931398748181818
00:08:33.140 --> 00:08:35.492 our best clinical models based on
NOTE Confidence: 0.931398748181818
00:08:35.492 --> 00:08:38.057 PSA Gleason score and stage actually
NOTE Confidence: 0.931398748181818
00:08:38.057 --> 00:08:40.372 performed quite model only modestly
NOTE Confidence: 0.931398748181818
00:08:40.372 --> 00:08:43.575 with C indices ranging from .52 to 0.7?
NOTE Confidence: 0.931398748181818
00:08:43.575 --> 00:08:45.345 So we’re really not meeting the
NOTE Confidence: 0.931398748181818
00:08:45.345 --> 00:08:47.368 mark yet and has significant ground
NOTE Confidence: 0.931398748181818
00:08:47.368 --> 00:08:49.650 to cover in guiding our patients.
NOTE Confidence: 0.880488586363636
00:08:52.070 --> 00:08:53.402 The questions that we want to
NOTE Confidence: 0.880488586363636
00:08:53.402 --> 00:08:57.283 know are actually very practical.
NOTE Confidence: 0.880488586363636
00:08:57.283 --> 00:08:59.450 For example, how likely is a patient
NOTE Confidence: 0.880488586363636
00:08:59.450 --> 00:09:01.910 cancer to spread if not treated,
NOTE Confidence: 0.880488586363636
00:09:01.910 --> 00:09:04.648 and can treatment be given in time?
NOTE Confidence: 0.880488586363636
Due to a very high prevalence of prostate cancer and its desperate decisional burden, there is 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.
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

So all of these tests are independently provide prognostic value compared to the standard of care variables such as PSA, Gleason, score, and clinical stage.

The disciple classifier is now the best studied and has been validated as both a prognostic and predictive marker.

In one retrospective study where the decipher scores were calculated based on archival FFP specimens, patients in the highest group faced substantially greater risk of metastatic progression after treatment. 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, 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 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. Patricia Re medical care that have previously been defined and
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 is generally not needed. And these tests are very much discretionary at the discretion of the position of the physician. So to answer the question about uptake, we evaluated trends and testing at the HRR level again. In addition to evaluating the presence of regional variation, we sought to also understand similarities among regions, and we use something called group based trajectory modeling perform of finite mixture modeling to identify 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 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
our guidelines and care practices.

So understanding that the clinical landscape is changing with the integration of new tools, we also wanted to understand the relation of taste testing to actual clinical management received by patients. But doing this experimentally is actually difficult in observation. ULL data, given the absence of granular clinical information and the absence of randomization, a common theme in this work is seeking therefore to understand and account for. These unmeasured bias is associated with
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
00:17:29.290 --> 00:17:32.291 receipt of a prostate MRI and initial
00:17:32.291 --> 00:17:34.215 observation for prostate cancer.
00:17:34.220 --> 00:17:36.760 And assess the association using
00:17:36.760 --> 00:17:38.284 conventional logistic regression
00:17:38.284 --> 00:17:40.319 and propensity score matching.
00:17:40.320 --> 00:17:44.343 In these analysis,
00:17:44.343 --> 00:17:46.442 we consistently found a strong association
00:17:46.442 --> 00:17:48.809 with an odds ratio of nearly two.
00:17:52.050 --> 00:17:55.860 Taking advantage of the substantial
00:17:55.919 --> 00:18:00.263 adoption of prostate MRI genomic testing
00:17:55.919 --> 00:17:57.539 that we saw in earlier studies,
00:17:57.540 --> 00:18:00.263 we wanted to study whether a region’s
00:18:00.263 --> 00:18:02.786 was also associated with changes in
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

And we sought to test the hypothesis that regions with high levels of

and genomic testing had greater changes favoring observation

And what we found was that those eight hours in the highest quartile

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 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
extrapolate these to patient effects,

but I think the consistency of these

associations and the practical

observation that there seems to be

a certain type or inclination of

institutions or providers who are much

more invested in the idea of surveillance,

suggests that these two may go hand in hand.

Another major focus of our work has

been to understand the experiences that

patients with prostate cancer have.

When using these patient facing tools.

Through in-depth interviews, we’ve also

specifically focused on this point.

And would speak and when

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, 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 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. A nearly two fold greater risk of prostate cancer death. One mechanism through which differences in outcome might occur is less
00:21:12.334 --> 00:21:14.704 access and less use of diagnostic
NOTE Confidence: 0.907213545333333
00:21:14.704 --> 00:21:16.864 technologies involved in the timely
NOTE Confidence: 0.907213545333333
00:21:16.864 --> 00:21:19.144 detection of potentially lethal cancers.
NOTE Confidence: 0.907213545333333
00:21:19.150 --> 00:21:20.714 In our earliest work,
NOTE Confidence: 0.907213545333333
00:21:20.714 --> 00:21:22.278 we identified substantially lower
NOTE Confidence: 0.907213545333333
00:21:22.278 --> 00:21:23.949 use of prostate MRI,
NOTE Confidence: 0.907213545333333
00:21:23.950 --> 00:21:26.670 even adjusting for clinical characteristics
NOTE Confidence: 0.907213545333333
00:21:26.670 --> 00:21:29.390 among black versus white patients.
NOTE Confidence: 0.907213545333333
00:21:29.390 --> 00:21:32.270 38% lower odds of prostate MRI
NOTE Confidence: 0.907213545333333
00:21:32.270 --> 00:21:35.318 use in in patients with low
NOTE Confidence: 0.907213545333333
00:21:35.318 --> 00:21:37.176 risk prostate cancer and although
NOTE Confidence: 0.907213545333333
00:21:37.176 --> 00:21:38.468 there are stark disparities,
NOTE Confidence: 0.907213545333333
00:21:38.470 --> 00:21:40.130 there are also very market
NOTE Confidence: 0.907213545333333
00:21:40.130 --> 00:21:41.126 differences by region.
NOTE Confidence: 0.907213545333333
00:21:41.130 --> 00:21:42.288 So, for example,
NOTE Confidence: 0.907213545333333
00:21:42.288 --> 00:21:44.604 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 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. 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 is fewer diagnosis of low risk prostate cancer through the use of refined pre biopsy
00:24:01.286 --> 00:24:03.636 decision tools such as prostate MRI
00:24:03.636 --> 00:24:06.146 and other biomarkers with better
00:24:06.146 --> 00:24:08.638 specificity for high risk disease.
00:24:08.640 --> 00:24:10.356 But among patients with prostate cancer,
00:24:10.360 --> 00:24:12.445 we've also identified gaps in
00:24:12.445 --> 00:24:14.530 access comprehension and support for
00:24:14.601 --> 00:24:16.877 patients undergoing complex testing.
00:24:16.880 --> 00:24:17.964 To close this gap,
00:24:17.964 --> 00:24:19.590 I think that multifaceted efforts are
00:24:19.644 --> 00:24:21.330 needed to help improve the consistency
00:24:21.330 --> 00:24:23.278 and quality of care that we deliver,
00:24:23.280 --> 00:24:25.232 and this is going to be a clear
00:24:25.232 --> 00:24:27.367 focus of ours in the years to come.
00:24:27.370 --> 00:24:29.236 There are also clear opportunities to
00:24:29.236 --> 00:24:31.304 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
can put it in the chat and I’ll I’ll ask a question while we’re waiting to see what people have. So is getting an MRI in it of itself something that leads to better care or is it a marker of doctors who provide a different kind of care? Yeah, it’s that’s really. I think that the main question we’re wrestling with is probably a little bit of both. I mean, I think that the MRI you know if MRI is not even on the table for you, you’re probably receiving one type of care.
00:26:34.810 --> 00:26:36.430 But I think but you know,
NOTE Confidence: 0.743726158
00:26:36.430 --> 00:26:38.565 with these very powerful tools you can,
NOTE Confidence: 0.743726158
00:26:38.570 --> 00:26:39.365 we can make.
NOTE Confidence: 0.743726158
00:26:39.365 --> 00:26:41.573 We can go in the wrong direction very
NOTE Confidence: 0.743726158
00:26:41.573 --> 00:26:43.925 easily because all of a sudden you have.
NOTE Confidence: 0.743726158
00:26:43.930 --> 00:26:46.016 A vast amount of data and one
NOTE Confidence: 0.743726158
00:26:46.016 --> 00:26:48.052 potential concern is that we may
NOTE Confidence: 0.743726158
00:26:48.052 --> 00:26:49.484 overestimate risk because we’re
NOTE Confidence: 0.743726158
00:26:49.484 --> 00:26:52.027 finding you know things that we never
NOTE Confidence: 0.743726158
00:26:52.027 --> 00:26:53.782 found before and then therefore,
NOTE Confidence: 0.743726158
00:26:53.790 --> 00:26:56.190 patients veer off the path of
NOTE Confidence: 0.743726158
00:26:56.190 --> 00:26:57.790 surveillance because you’ve technically
NOTE Confidence: 0.743726158
00:26:57.850 --> 00:26:59.955 have found something that you had
NOTE Confidence: 0.743726158
00:26:59.955 --> 00:27:02.160 to work very hard to look for.
NOTE Confidence: 0.743726158
00:27:02.160 --> 00:27:02.530 Sure,
NOTE Confidence: 0.845781166
00:27:02.770 --> 00:27:05.880 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 this specifically on prostate cancer, although it wasn’t written that way.

Well, yeah, thank you. I mean, 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,
that you know major centers.

You know it’s this MRI and genomic testing are really an early adopter phenomenon. So I think we have a disproportionate influence.

I think that in Los Angeles, certain medical centers probably also have a disproportionate influence, so all the more reason to be very circumspect and proactive in when we roll the when we roll these things out.

Great, well, I think we’re going to move
on to our next speaker, Michael. Thank you very much.

So our next speaker is Carlos Fernandez Fernando, who is the Anthony and Brady Professor of Comparative medicine and pathology. He studied biochemistry and molecular biology at the University, and received his PhD at Hospital, and did his postdoctoral work with Doctor William. Tessa here at Yale. His first position was...
00:29:12.876 --> 00:29:14.818 faculty position was at NYU,
NOTE Confidence: 0.7774961625
00:29:14.820 --> 00:29:18.558 and then he returned to Yale where
NOTE Confidence: 0.7774961625
00:29:18.558 --> 00:29:21.474 his research seeks to identify novel
NOTE Confidence: 0.7774961625
00:29:21.474 --> 00:29:24.549 mechanisms by which cholesterol and
NOTE Confidence: 0.7774961625
00:29:24.549 --> 00:29:27.900 lipoprotein metabolism are regulated
NOTE Confidence: 0.7774961625
00:29:27.900 --> 00:29:30.652 and without further comments,
NOTE Confidence: 0.7774961625
00:29:30.652 --> 00:29:33.260 I’m going to turn this over to Carlos.
NOTE Confidence: 0.81487696
00:29:47.710 --> 00:29:49.030 You’re still on mute.
NOTE Confidence: 0.8595668
00:30:00.030 --> 00:30:03.156 OK, now I see this working well
NOTE Confidence: 0.822809175555556
00:30:03.790 --> 00:30:05.350 so we can’t see your slides
NOTE Confidence: 0.822809175555556
00:30:07.250 --> 00:30:10.698 at this month. Now we can
NOTE Confidence: 0.8334467725
00:30:07.250 --> 00:30:10.698 OK. Thanks very much.
NOTE Confidence: 0.8334467725
00:30:10.700 --> 00:30:13.388 I really appreciate the invitation for
NOTE Confidence: 0.8334467725
00:30:13.388 --> 00:30:15.660 for giving the presentation today.
NOTE Confidence: 0.8334467725
00:30:15.660 --> 00:30:17.604 Let me put this in full skin, uhm?
NOTE Confidence: 0.8334467725
55
As you mentioned, I’m not a.
I didn’t never study much about 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, PSD.
As 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 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. Around that time, the group from Matthias Eichenwald, who had been working on obesity driving tumor formation.
00:33:27.630 --> 00:33:30.290 airing in the Cancer Research Center in Heidelberg,
00:33:30.290 --> 00:33:35.160 published this novel model of obesity,
00:33:35.160 --> 00:33:38.404 driving part of local phenomena that was based in feeding the mice without killing,
00:33:38.404 --> 00:33:42.360 defeating high fat diet.
00:33:42.360 --> 00:33:44.800 In the upper panel you see a number of papers that this group publishes recently using this.
00:33:44.800 --> 00:33:47.418 This model of the disease.
00:33:47.420 --> 00:33:49.580 It’s a pretty good model in our opinion, because, uh,
00:33:49.580 --> 00:33:51.916 the mice develop all the features that help the people that develop obesity,
00:33:51.916 --> 00:33:54.836 This model of the disease.
00:33:54.840 --> 00:33:55.448 It’s a pretty good model in our opinion,
00:33:55.448 --> 00:33:58.540 because, uh,
00:33:58.540 --> 00:33:59.118 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 fed 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
00:35:18.042 --> 00:35:20.571 the war from from Jonathan and and
NOTE Confidence: 0.6054106485
00:35:20.571 --> 00:35:23.300 this is in the upper left corner.
NOTE Confidence: 0.6054106485
00:35:23.300 --> 00:35:25.848 You see the loyal to experiments that
NOTE Confidence: 0.6054106485
00:35:25.848 --> 00:35:28.785 we did here and all the analysis that
NOTE Confidence: 0.6054106485
00:35:28.785 --> 00:35:31.954 we did in every day and in every time
NOTE Confidence: 0.6054106485
00:35:31.954 --> 00:35:33.986 point I’m going to show you only a
NOTE Confidence: 0.6054106485
00:35:33.986 --> 00:35:36.435 few data about the this the whole study.
NOTE Confidence: 0.6054106485
00:35:36.440 --> 00:35:39.092 But then we actually collect
NOTE Confidence: 0.6054106485
00:35:39.092 --> 00:35:41.252 issues at three six 12115 months
NOTE Confidence: 0.6054106485
00:35:41.252 --> 00:35:42.656 to do lipidomic analysis.
NOTE Confidence: 0.6054106485
00:35:42.660 --> 00:35:44.268 Public functionary sequence
NOTE Confidence: 0.6054106485
00:35:44.268 --> 00:35:45.768 in single sequencing.
NOTE Confidence: 0.6054106485
00:35:45.768 --> 00:35:47.480 Oregon municipal Chemistry not
NOTE Confidence: 0.6054106485
00:35:47.480 --> 00:35:50.051 only for delivery but also for
NOTE Confidence: 0.6054106485
00:35:50.051 --> 00:35:52.211 other tissues and also we track
NOTE Confidence: 0.6054106485
00:35:52.211 --> 00:35:54.144 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
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 recapitated 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. And as you can see here, this might develop significant accumulation of lipids. You see the ballooning also there 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,

We notice that after 12 months,
00:38:14.332 --> 00:38:15.941 people of the development of
00:38:15.941 --> 00:38:17.457 commercial was quite restricted.
00:38:17.460 --> 00:38:19.816 We found seven of the 39 mice
00:38:19.816 --> 00:38:22.324 developed tumors and all of these
00:38:22.324 --> 00:38:25.330 correlate with the more or less with
00:38:25.330 --> 00:38:27.420 the simulating alpha fetal protein
00:38:27.499 --> 00:38:30.037 levels in circulation of the mice.
00:38:30.040 --> 00:38:32.990 As you can see in the in the 15 months group.
00:38:35.540 --> 00:38:38.235 The incidence of the two more simply
00:38:38.235 --> 00:38:40.810 significantly many of the money the mice
00:38:40.810 --> 00:38:42.980 around 50% of the mice develop tumors,
00:38:42.980 --> 00:38:44.558 and also they feel levels are
00:38:44.558 --> 00:38:46.470 very hot in the right panels you
00:38:46.470 --> 00:38:47.850 can see a representative image,
00:38:47.850 --> 00:38:49.722 so the kind of tumors that you observed
00:38:30.040 --> 00:38:32.990 As you can see in the in the 15 months group.
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. And you know so with you. We're still first delineated, 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 1st. 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. Marissa little bit the. The son of the first experiment we did, we took a pentagon 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. In the left plot the thing that you see here is all the single events thereby shown by dots that corresponding are grouped in different colors that correspond with the different cellular populations that you all share in the livers. 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 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 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 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 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 --> 00:47:40.485 two more oligoclonal or monoclonal.
NOTE Confidence: 0.667202877047619
00:47:40.485 --> 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 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.
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. Then then Jonathan went ahead.
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 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

NOTE Confidence: 0.80565626

89
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, 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
abundant in the epidermis is highly
expressed. Their win was was found.
Uhm, 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 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 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 we were not expecting such 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
incidents in significantly reviews

which we only observe only 6 of 20.

Did not work.

Even more remarkable is when we actually measure that replating anything this nice.

You can see that.

There you see levels increase in the mice that progress towards the disease,

but those miles adapted with the.

Incubator not only you stop the progression,

but you see also a regulation of these bodies.

Then this telling us that this track price not only preventing 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.

He’s also a number of.

And all that analysis in in human cells.

Then this is the the study that he did in

in age who is 7 human local cinema line.

And try to go even induce you know deeper

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 upregulated 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 long 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 very clear data showing
that the oxidative stress also in the US here stressing these tales.

Unluckily, this induced cell death in this match. In there in these two more cells.

This is the heat map from scientist pathways. You can see that the pair UTR padway being significantly unregulated in the mice.

And just to finish, because I’m running out of time, yes, the last couple of slides this is.

An example of some of the experiments he did here, and when we did with the cells and she very nicely over with very bad way. And not only that,
but when he did also understanding here
with PIE 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
we know that they
can have some after that fact,
and we’re trying to combine this with the
genomic data just to demonstrate the role.
00:58:15.190 --> 00:58:17.914 Sucky role of fighting into more
NOTE Confidence: 0.797661448
00:58:17.914 --> 00:58:19.690 pressing then this is a little
NOTE Confidence: 0.797661448
00:58:19.690 --> 00:58:21.626 bit the summary of this of this
NOTE Confidence: 0.797661448
00:58:21.626 --> 00:58:23.294 work I'm doing so many things, Trump
NOTE Confidence: 0.63618844
00:58:23.300 --> 00:58:25.793 but the thing that we. Trump
NOTE Confidence: 0.63618844
00:58:25.793 --> 00:58:27.958 carries that the suppression of.
NOTE Confidence: 0.4711104252
00:58:30.050 --> 00:58:33.210 M accumulation of fatty acid.
NOTE Confidence: 0.4711104252
00:58:33.210 --> 00:58:35.454 Resulting in increasing years, just new
NOTE Confidence: 0.4711104252
00:58:35.454 --> 00:58:37.858 Paris Ponce leading to Apple classes.
NOTE Confidence: 0.4711104252
00:58:37.858 --> 00:58:41.706 This is only like 50% on the part of
NOTE Confidence: 0.4711104252
00:58:41.706 --> 00:58:44.615 the story because the thing that he
NOTE Confidence: 0.4711104252
00:58:44.615 --> 00:58:47.345 Jonathan also observed here is that
NOTE Confidence: 0.4711104252
00:58:47.350 --> 00:58:50.570 not only the inhibitor has a very
NOTE Confidence: 0.4711104252
00:58:50.570 --> 00:58:54.020 important effect controlling the.
NOTE Confidence: 0.4711104252
00:58:54.020 --> 00:58:56.245 And the cancer cell metabolism
NOTE Confidence: 0.4711104252
00:58:56.245 --> 00:58:58.470 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. The 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,
00:59:38.880 --> 00:59:40.300 which is actually very interesting,
NOTE Confidence: 0.646646158235294
00:59:40.300 --> 00:59:41.820 is working in different ways,
NOTE Confidence: 0.646646158235294
00:59:41.820 --> 00:59:44.550 not only reacting in the counterfoils.
NOTE Confidence: 0.646646158235294
00:59:44.550 --> 00:59:48.033 But those show acting at the in the two
NOTE Confidence: 0.646646158235294
00:59:48.033 --> 00:59:51.679 more microenvironment at the level of the
NOTE Confidence: 0.646646158235294
00:59:51.680 --> 00:59:54.356 immune response within the two months.
NOTE Confidence: 0.646646158235294
00:59:54.360 --> 00:59:56.592 Then with this I would like to to
NOTE Confidence: 0.646646158235294
00:59:56.592 --> 00:59:58.419 finish the presentation again.
NOTE Confidence: 0.646646158235294
00:59:58.420 --> 00:59:59.920 I put them in capital letter.
NOTE Confidence: 0.646646158235294
00:59:59.920 --> 01:00:02.720 Jonathan served all the credit for this work.
NOTE Confidence: 0.646646158235294
01:00:02.720 --> 01:00:05.904 He took the challenge to do it and.
NOTE Confidence: 0.646646158235294
01:00:05.910 --> 01:00:08.610 Did many models to study this
NOTE Confidence: 0.646646158235294
01:00:08.610 --> 01:00:10.410 and employing novel technology,
NOTE Confidence: 0.646646158235294
01:00:10.410 --> 01:00:12.797 then then he really did the the
NOTE Confidence: 0.646646158235294
01:00:12.797 --> 01:00:14.873 person who decided credit for this
NOTE Confidence: 0.646646158235294
01:00:14.873 --> 01:00:16.798 work and also my laboratory has
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. 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 cathedral 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 think and I think it’s a great question because you know today. Then I want to point out that we did this experiment with with money. Then I want to point out that 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 females 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 know, I know,
I am much more aware about the literature in human, I should be more aware now after I sent him again, I will read more, but at least in mouse models OK? Because being shown that in in the in other models the females asked happen here develop significantly as less tumors, and this has been associated in part to the adipose tissue production of adiponectin and another or modes. Then it’s not clear whether this is translated to human, but looks at all the depots that are different in male and female appears
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,

Yeah?

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.