Is a special lecture in our Yale Cancer Center Grand Rounds series and it’s the Blanche Tolman lecture series. So this lecture series was established in 2012 by Doctor Marvin Sears, who I believe will be attending today as well.

Dr. Sears was a long time chair and founder of Thermology and Visual Sciences at Yale and the lecture was established in honor of his mother, Blanche Tallman, who passed away from acute myeloid leukemia.
So to our delight, this was the first lecture series at year dedicated solely to hematologic malignancies and it continues to bring to Yale pioneers that have made major contributions to our understanding of the current trends and hematologic malignancies. So it is an absolute pleasure to introduce the actor Irene Gabriel today as our special lecturer. So Doctor Gabriel is professor of medicine at Harvard Medical School. She received her MD from Cairo University School of Medicine in Egypt. And she then completed her internal
medicine training at Wayne State University and her hematology oncology subspecialty training at Mayo Clinic College of Medicine. In 2005, she joined in a Farber Cancer Institute in the field of Waldenstrom’s Macroglobulinemia and a multiple myeloma. So doctor Gabrielle, as you will all see, has risen to become one of the world’s leaders in the democratic field. Not only has she advanced major novel treatments to the clinic, but she now also focuses on early
detection and interception to prevent.

Regression to full blown multiple myeloma.

Doctor Gabriel has a broad background in the biology of multiple myeloma and in the bone Marinette so important in the focus on M gas and smoldering myeloma and again preventing disease and her her research knowledge expertise allow us to define both cell autonomous and bone marrow age dependent and also genetic and epigenetic mechanisms of disease progression. And we couldn’t be more excited to hear your talk today.

So welcome we wish we were in person but.
This is still wonderful.
And at least we didn’t have to cancel.
Yes. Well, thank you so much,
Stephanie. And as you said,
it’s really a pleasure and honor to be here.
And I’m sorry that it’s not in person,
but it’s New England and we all
know how to deal with that, I guess.
So I’ll take you through a little bit
of what we do in the lab and how we
translated it into the clinic on the
promise of early detection and interception.
These are these are my conflicts of interest.
So I’ll just start with a simple
question that many of us ask ourselves.
In general, in every Cancer Center when you see patients, it’s because they either had symptoms and they want to see their primary care doctor or by accident, something happened in their blood works. They had a little bit of anemia, a little bit of a higher white count which led to the diagnosis of cancer and then they get referred to you. But if you think about it, this means that we are waiting for things to happen and then. We react to cancer and by chance some of those made by good luck
00:03:06.617 --> 00:03:08.694 have an early cancer and we can
diagnose it early and we can cure it.

00:03:11.020 --> 00:03:13.436 But many of them actually have stage three,
stage four cancer.

00:03:13.440 --> 00:03:14.211 And we do sit down with them and
say we may give you some treatment,
but we may not cure the disease.

00:03:16.332 --> 00:03:21.176 And in fact if you think about it,
pharmaceutical companies as well
as cancer centers put millions and
billions of dollars into developing
therapies that can change to survival
of metastatic cancer by three or four
months and we consider that. Success.

00:03:21.180 --> 00:03:22.760 pharmaceutical companies as well

00:03:22.760 --> 00:03:25.130 as cancer centers put millions and

00:03:25.196 --> 00:03:27.081 billions of dollars into developing

00:03:27.081 --> 00:03:29.370 of metastatic cancer by three or four

00:03:29.370 --> 00:03:31.722 months and we consider that. Success.

00:03:31.722 --> 00:03:33.608 So what can we do to change that?
How can we become less reactive to cancer and be more proactive to cancer, trying to find it early before it becomes symptomatic, trying to define it early. And then by doing that you can intervene early and make a difference in the survival of those patients? Now I would probably say that myeloma is a great example of that as a potential model system for early detection and interception. We know that myeloma has a well known clinically defined precursor condition, monoclonal gammopathy of undetermined significance and yet another monclonal gammopathy of undetermined significance and then yet another
NOTE Confidence: 0.890911035714286
00:04:09.431 --> 00:04:11.778 stage of the disease that progresses
NOTE Confidence: 0.890911035714286
00:04:11.778 --> 00:04:13.598 just before the active cancer,
NOTE Confidence: 0.890911035714286
00:04:13.600 --> 00:04:14.740 sort of a stage one,
NOTE Confidence: 0.890911035714286
00:04:14.740 --> 00:04:16.504 stage two breast cancer if you
NOTE Confidence: 0.890911035714286
00:04:16.504 --> 00:04:18.935 want to call it and that’s the
NOTE Confidence: 0.890911035714286
00:04:18.935 --> 00:04:20.123 asymptomatic smoldering myeloma
NOTE Confidence: 0.890911035714286
00:04:20.123 --> 00:04:22.609 Now I was lucky enough to be.
NOTE Confidence: 0.890911035714286
00:04:22.610 --> 00:04:24.658 Trained by Bob Kyle at Mayo Clinic who
NOTE Confidence: 0.890911035714286
00:04:24.658 --> 00:04:26.169 actually coined both of those terms,
NOTE Confidence: 0.890911035714286
00:04:26.170 --> 00:04:28.010 monoclonal gammopathy of undetermined
NOTE Confidence: 0.890911035714286
00:04:28.010 --> 00:04:29.850 significance and smoldering myeloma.
NOTE Confidence: 0.890911035714286
00:04:29.850 --> 00:04:31.894 And he had this amazing vision because
NOTE Confidence: 0.890911035714286
00:04:31.894 --> 00:04:33.897 he thought that when he described
NOTE Confidence: 0.890911035714286
00:04:33.897 --> 00:04:35.325 those asymptomatic patients who
NOTE Confidence: 0.890911035714286
00:04:35.325 --> 00:04:37.704 are just walking around with a very
NOTE Confidence: 0.890911035714286
small tiny monoclonal protein that they should actually be watched carefully and we they may actually progress to develop the disease. And in fact, him and Jan Waldenstrom had a big discussion where Jan Waldenstrom wanted to call it benign gammopathy because those patients. Yet Bob Kyle was so good in thinking ahead and thinking that there is a potential of cancer development and he coined the name of undetermined significance to give it that
sense of urgency, of understanding who would progress in their lifetime and potentially preventing it. And indeed, even the name smouldering myeloma gives you that urgency that it’s going to be on fire very soon. So let’s do something about it. So indeed he had that vision. As we should think of the mechanisms of disease progression in asymptomatic people and potentially intercepting early. Now in the older days we didn’t have good drugs, we had melphalan,
Prednisone, fat chemotherapy.

So maybe intercepting early May not make sense.

And indeed the trend or the standard of care was watch and wait until people have symptoms and end organ damage and then we treat them because we have palliative care and myeloma survival is only three to five years, but now we have 30 new drugs approved.

For myeloma, we have amazing responses and the question is truly can we change that thinking of disease interception at an earlier time point?

Now the other important piece to
think about is myeloma is more common in African Americans and people of African descent 2 times or even higher, more common, more common to happen at an earlier younger age. In fact, we know that myeloma is more common because they haven’t earlier stage of development, not because usually of an mgus transition to myeloma, not that we know of, but we don’t think that there is a faster transition from mgus to myeloma. So really understanding what causes.
Early development of MGUS in an African American population at the younger age could. That you help us understand why they've developed Milo memoir, but also intercepting it early because most of those patients, by the time they're diagnosed, they're either misdiagnosed because anemia is very common in African Americans or because of renal failure. And again, renal failure is more common. So they are getting misdiagnosed. They don't have the World Cup. And even when they have the World Cup and the disease assessment,
they do not get the access to clinical trials and to car T and to transplant and all of the options that we have, so the survival of myeloma in African Americans. Unfortunately, it’s still very poor. Despite all of the amazing advances we have, we still have a huge discrepancy there. So potentially closing that gap would be critical for us to understand how to change the survival of Milo. So with that in mind, our hypothesis really our model is why are we doing it any different than other cancers?
If you think of breast cancer for example, you screen early because cancer screening saves lives. And I would tell you that the blood test for a serum protein Electro. Races and monoclonal protein is much easier, more sensitive and more specific and potentially much better for us because I would rather get a blood sample done than mammography or colonoscopy. It’s much easier to do. But even though we with that, we don’t screen for blood cancers. They’re easy to screen but we don’t screen for them. And even when we find the monoclonal...
gammopathy is when I find MGUS, and it’s very common in the general population, 3 to 5% over the age of 50 or even when I find smoldering myeloma. The standard of care to date is still telling them watch and wait until you have anemia, renal failure, fractures in your bones or lesions in your bones, and high calcium, what we call the crab criteria. That would be just like telling a woman with breast cancer, DCIS, or stage one, stage two breast cancer. You know what, you’re asymptomatic. Go watch and wait until you
have metastases everywhere,

and then I'll treat you.

Now you'll have a lawsuit when that case.

So why are we not getting lawsuits?

Myeloma, when we do that exact same idea.

So really we need to rethink the way

we think of treatment of myeloma and

retrain ourselves to think that’s not

actually the right way of thinking.

Maybe again,

30-40 years ago when we only

had melphalan at Prednisone,

it was a good idea.

Right now it may not be a good idea to

watch and wait for those patients or as
my patients call it, watch and worry.

So how do we change that?

We have three different areas or pillars of work that we’re doing.

Both in the lab and in the clinic we said, well, let’s detect early,

let’s screen early because currently most patients with mgus and smoldering myeloma are found purely incidentally.

let’s really understand better when you screen those patients,

what is the prevalence but also who will progress and who will not in their lifetime.

The next question is let’s risk stratify those patients.
Not every MGUS we diagnose will go on to progress to myeloma. So the question is who in their lifetime will progress to myeloma because these are the ones you want to treat. And the others, you want to tell them you're OK, you're going to live a normal life without having to develop myeloma and that differential is critical so that you can truly personalize that risk stratification for patients. And then the third one is, unless you know that you can change the survival of those patients, unless you can really intercept
and change their survival,

why are you screening for it? Because otherwise you're causing anxiety and no change.

So truly I reverse it usually and say interception is more important because without interception we should not be.

Training and we should not be stratifying those patients.

So let’s start with early detection and why it matters. We have seen lots of nationwide studies, the first one in Olmsted County where we indeed know the prevalence of emcas in the general population.
3 to 5% over the age of 50.

But that was found in mostly Caucasian population in the area of Olmsted County in Minnesota.

So the question was, can we really detect in a much more sensitive way than serum protein electrophoresis?

And in the high risk population not in the general population, what is the prevalence of monoclonal hemoptysis and does a treaty occur in a younger age in African Americans? So there has been some studies indicating that people of African descent as well as people with a first degree family member.
are likely two to three times higher,
have a higher chance of developing myeloma.
So we wanted to ask why in high risk screen population and this was started four years ago with the help of a stand up to cancer Dream Team. Application where we started to say let’s screen in the US for myeloma and we said we will do it nationwide. So it’s online. 
As you can see here, you get a QR code and if you meet the eligibility criteria, you can sign up wherever you are and we send you a kit at home.
You go to a quest diagnostic and you send us the blood sample. And the second thing we did is we did it by mass spectrometry, which is much more sensitive than serum protein electrophoresis. Now to do that effort, we said that we want to screen 30,000 individuals to potentially get 10% screen positive because that’s the number that from our preliminary data indicated we will have a positive number. And then we will follow those 3000 people to understand genomics, genetics mechanisms of disease progression, immune microenvironment or non immune microenvironment or non immune
epidemiological causes like obesity,
inflammation, autoimmune diseases and of course
develop therapeutics and imaging modalities for those.
People now as we started, we really had to learn to have boots on the ground to really do the effort
because if you talk to anyone about myeloma, even the African American population would tell you,
I didn’t even know.
There is more common in the black community than in the white population.
So we have to do effort to even educate
what is myeloma to gain the trust of the African American population and then start screening them. And that was a lot of effort from a team that we hired, just going to church events, going to healthcare. understanding how to work with our Congress people like Ayanna Presley here and of course COVID hit and all our effort got shot down because you cannot do that on zoom. So it really took us a lot of effort to try and restart all of this. And indeed we just started to go back
NOTE Confidence: 0.896335315517241
00:12:54.082 --> 00:12:56.100 to health fair events and restarting it
NOTE Confidence: 0.896335315517241
00:12:56.100 --> 00:12:58.370 while while we were in COVID we said,
NOTE Confidence: 0.896335315517241
00:12:58.370 --> 00:13:01.170 well let’s look at datasets and samples
NOTE Confidence: 0.896335315517241
00:13:01.170 --> 00:13:04.369 that are already collected in other cohorts.
NOTE Confidence: 0.896335315517241
00:13:04.370 --> 00:13:06.349 And this is when we turned to
NOTE Confidence: 0.896335315517241
00:13:06.350 --> 00:13:07.590 the mass general, Brigham,
NOTE Confidence: 0.896335315517241
00:13:07.590 --> 00:13:08.520 so mass general.
NOTE Confidence: 0.896335315517241
00:13:08.520 --> 00:13:10.722 Brigham is a huge sample collection
NOTE Confidence: 0.896335315517241
00:13:10.722 --> 00:13:13.252 study that’s been going on now for the
NOTE Confidence: 0.896335315517241
00:13:13.252 --> 00:13:15.568 last 10 years with samples as well
NOTE Confidence: 0.896335315517241
00:13:15.568 --> 00:13:17.920 as of course clinical data annotation
NOTE Confidence: 0.896335315517241
00:13:17.991 --> 00:13:20.097 from all of the partners healthcare
NOTE Confidence: 0.896335315517241
00:13:20.097 --> 00:13:22.587 system or MGB as we call it now.
NOTE Confidence: 0.896335315517241
00:13:22.590 --> 00:13:25.146 So we collected the same criteria,
NOTE Confidence: 0.896335315517241
00:13:25.150 --> 00:13:27.665 African-American or people of first
NOTE Confidence: 0.896335315517241
degree family members from 80,000 samples that we have in MGB and total enrolled so far is 12,592. We also opened a promised South Africa one where actually they’re getting almost to 2000 samples now that they’ve recruited prospectively. And we’re also going on into opening it now in Israel because of the family histories as well as many other countries that we can do. And we were screening in my lab almost 1000 samples a week and we can do even more because mass spectrometry can get to a higher throughput level.
and you can then get detection of monoclonal proteins as well as light. Machines in a very quantitative way compared to serum protein electrophoresis. In fact, we set up the normals for binding site and now we are part of their FDA approval hopefully soon for binding site. So these are just some of the numbers showing you from MGB from promised South Africa and promised us. But this is the largest number of African Americans who have been screened to date as well as people with family history and it was interesting when we saw families with 567 members.
We have MGUS and myeloma and lymphoma. Now you start asking questions of germline events of events that really can lead to that development in an early risk population. This is the paper that we published last year just for the 1st 7000 people and now we’re actually going on for the larger cohort. And as you can see here, the people with a family history of a blood cancer were 3866 and people of African descent or blacks were 2439. This is the mass spectrometry and I call this the Christmas tree. And this is the mass spectrometry and I call this the Christmas tree. So mass spectrometry is quantifiable.
and you can also reflect it to LCMS to give you a further detection of the monoclonal protein. So all of these were truly monoclonal proteins that were quantified and verified. What we found is anything above 1 gram per liter is something that you can also detect by serum protein electrophoresis because we did spap the traditional method in the sum of the samples or in almost all of the samples. If we did anything below that at .2 grams per liter, you could potentially also detected by immunofixation.
but of course you have quantification and much more sensitivity by the mass spectrometry. So we kept those terms as they are. But interestingly and I still remember it when we got the first data because we couldn’t believe it, we found another 20% of people with very small monoclonal gammopathy that were much lower than the level that we can detect by immunofixation. And at first we said, well these are probably errors, so we reconfirmed them. Maybe these are people who have infections, so we rescreen them.
We kept going on to try and understand what this is and we finally said, well no one has they’ve ever discovered very small monoclonal proteins. Let’s let the research tell us what it is. Now we wanted to term this something separate that mgus because we really didn’t know if this is mgus or not. So we called it mgip, monoclonal gammopathy of indeterminate potential alert ship. Don’t let him have the praises. And the story goes that David Steensma
00:16:43.977 --> 00:16:47.057 is the one who coined the name chip.
NOTE Confidence: 0.77078895047619
00:16:47.060 --> 00:16:48.356 And I saw him once and he said,
NOTE Confidence: 0.77078895047619
00:16:48.360 --> 00:16:50.800 well I called chip based on M Gus.
NOTE Confidence: 0.77078895047619
00:16:50.800 --> 00:16:52.200 I was trying to imitate
NOTE Confidence: 0.77078895047619
00:16:52.200 --> 00:16:53.600 what doctor Kyle had done.
NOTE Confidence: 0.77078895047619
00:16:53.600 --> 00:16:55.496 So now we called M give based on
NOTE Confidence: 0.77078895047619
00:16:55.496 --> 00:16:57.990 chip and it keeps going round and
NOTE Confidence: 0.77078895047619
00:16:57.990 --> 00:16:59.558 round in hematological malignancies.
NOTE Confidence: 0.77078895047619
00:16:59.558 --> 00:17:01.729 But what is this chip and what is this
NOTE Confidence: 0.77078895047619
00:17:01.729 --> 00:17:04.276 mgus prevalence in this high risk population?
NOTE Confidence: 0.77078895047619
00:17:04.280 --> 00:17:06.114 So you can see here by age
NOTE Confidence: 0.77078895047619
00:17:06.114 --> 00:17:07.780 that mgip is very common,
NOTE Confidence: 0.77078895047619
00:17:07.780 --> 00:17:09.550 almost 20% of the population.
NOTE Confidence: 0.77078895047619
00:17:09.550 --> 00:17:10.522 It increases with age,
NOTE Confidence: 0.77078895047619
00:17:10.522 --> 00:17:13.004 but as you go on with age the M
NOTE Confidence: 0.77078895047619
00:17:13.004 --> 00:17:14.609 Gus proportion of those monoclonal
NOTE Confidence: 0.77078895047619
00:17:14.609 --> 00:17:16.522 gammopathy is increases more and then
NOTE Confidence: 0.77078895047619
00:17:16.522 --> 00:17:18.726 light chain mgus was actually a very
NOTE Confidence: 0.77078895047619
00:17:18.726 --> 00:17:20.606 small number in that population.
NOTE Confidence: 0.77078895047619
00:17:20.610 --> 00:17:24.514 If I just take a standard values 3% of
NOTE Confidence: 0.77078895047619
00:17:24.514 --> 00:17:26.224 the population in general population
NOTE Confidence: 0.77078895047619
00:17:26.224 --> 00:17:28.264 is what doctor Kyle had described
NOTE Confidence: 0.77078895047619
00:17:28.264 --> 00:17:30.490 before and that was based on Spep.
NOTE Confidence: 0.77078895047619
00:17:30.490 --> 00:17:33.255 If you double it because of the
NOTE Confidence: 0.77078895047619
00:17:33.255 --> 00:17:35.104 higher risk population which is
NOTE Confidence: 0.77078895047619
00:17:35.104 --> 00:17:37.455 true 6% in our population are espec
NOTE Confidence: 0.77078895047619
00:17:37.455 --> 00:17:40.178 positive and then if you look by mass.
NOTE Confidence: 0.77078895047619
00:17:40.180 --> 00:17:42.064 That trauma too because it’s much
NOTE Confidence: 0.77078895047619
00:17:42.064 --> 00:17:44.017 more sensitive and can get you
NOTE Confidence: 0.77078895047619
00:17:44.017 --> 00:17:46.018 immunofixation than we are 13% and
NOTE Confidence: 0.77078895047619
00:17:46.018 --> 00:17:48.566 that’s not even accounting for the mgip.
NOTE Confidence: 0.77078895047619
35
So a large proportion of our high risk individuals have mgus and we need to understand better why they have it, but also who would progress in their lifetime. Now in general all monoclonal gammopathy’s were associated with worse overall survival and it was not because of myeloma, it was also because of many autoimmune diseases, cardiovascular disease, many other lymphomas. So we started seeing maybe mgus and immune dysregulation in those patients may have other effects,
not just myeloma development.
And thus lead is leading us to understand more into correlations of mgus and chip mutations, both of them cause inflammation, potentially increased cardiovascular risk. We’re trying to understand how that regulates the immune system and immune aging, how it correlates with autoimmune diseases and so many other questions. But what we were intrigued by is those M Gibbs and why were they present in many of those people. And most of those M gifts were actually IG M Mgip, not IG or IGA.
So the first thing we said. Well, maybe it’s an isotype class switch. This is the precursor of myeloma and it’s IGM positive and then it’s class switches to IgG as it progresses and this is the first event that requires the mutations. The other possibility was maybe these are lymphomas and they secrete very low levels of IGM that’s non detectable by ssep and in general we don’t even screen for lymphomas by serum protein electrophoresis. So we’re under we’re not detecting enough of the cells and low grade. Performers and now we have a
technology that can be
more sensitive and indeed for us to
prove that, we took samples from healthy
donors from two people who have mgus,
one of them had mgus and mcgiff and
from 2 participants who had mgip.
And we did first single cell sequencing for VDJ,
so now for the BCR to see if
they have clonal BCR in those.
Patients and then of course we did
gene expression profiling afterwards
with the single cell RNA sequencing.

And what was surprising as you can see here for this patient for example,

they had one clone that was all VDJ, the same clone and you can see that in this patient all of those cells.

So this is single cell RNA sequencing and the blood,

all of the cells were for one clone only in that patient.

And then this second patient had two different clones as you can see one of them was very high which is the.

The red one here and then the second one here in the orange one.

And indeed we reconfirmed that
those patients, one of them was indeed an early CLL case because we did flow cytometry and because this patient had almost 60% of the cells are all clonal, we were able to do whole genome sequencing on that sample. And indeed it was an atypical lymphoma, likely a post germinal B cell lymphoma. Copy number alterations as you see here, chromosome 3, chromosome 18 with a gain.
00:20:59.960 --> 00:21:01.250 of those chromosomes.
NOTE Confidence: 0.87823653631579
00:21:01.250 --> 00:21:03.530 So indeed by both DNA,
NOTE Confidence: 0.87823653631579
00:21:03.530 --> 00:21:05.396 by protein level in flow cytometry
NOTE Confidence: 0.87823653631579
00:21:05.396 --> 00:21:07.228 and by RNA sequencing we were
NOTE Confidence: 0.87823653631579
00:21:07.228 --> 00:21:09.090 able to indicate that two of those
NOTE Confidence: 0.87823653631579
00:21:09.090 --> 00:21:10.249 cases were lymphomas.
NOTE Confidence: 0.87823653631579
00:21:10.250 --> 00:21:12.266 Now we’re expanding that cohort to
NOTE Confidence: 0.87823653631579
00:21:12.266 --> 00:21:13.981 another 4050 samples with single
NOTE Confidence: 0.87823653631579
00:21:13.981 --> 00:21:15.829 cell RNA sequencing and then it
NOTE Confidence: 0.87823653631579
00:21:15.829 --> 00:21:17.707 will be followed by DNA sequencing
NOTE Confidence: 0.87823653631579
00:21:17.707 --> 00:21:19.786 of course if we find this positive,
NOTE Confidence: 0.87823653631579
00:21:19.790 --> 00:21:22.286 but that opens the door for saying we
NOTE Confidence: 0.87823653631579
00:21:22.286 --> 00:21:24.610 can screen also for other lymphomas.
NOTE Confidence: 0.87823653631579
00:21:24.610 --> 00:21:25.940 And not just for myeloma.
NOTE Confidence: 0.87823653631579
00:21:25.940 --> 00:21:27.949 And the question is what are all
NOTE Confidence: 0.87823653631579
00:21:27.949 --> 00:21:29.600 of those monoclonal gammopathy is
doing in our general population.

So to answer some of those questions, we’re moving on to other bigger cohorts. So now we’re talking to the UK Biobank, they have a half a million samples that have been collected over 20 years. We’re talking to end Haynes and trying to get samples from NHANES as you can see here 7937 another 8000 and PLO another 14,000. We are also trying to see if we can get access to the million. Veterans project to all of us and many other cohorts that have already collected large numbers of samples.
to ask big questions of what is the prevalence in high risk population, but also what are those early monoclonal democracies doing to the general population. And then of course we have collaborations with all link to try and look at the protein level in those patients with proteomics. So the next step I’ll take you through is understanding mechanisms of disease progression. If you have mgus or smoldering myeloma, you want to know what is. My personal risk of going on to dissolve myeloma and I don’t
have in the slides here what we just published yesterday night, it just came out in Lancet hematology, a new dynamic model to understand risk of progression because we know that the current clinical criteria, 20% plasma cells in your bone marrow, 2 grams M spike, 20 light chain ratio for a smoldering myeloma are good but not good enough because they give you a 50% chance of progression in two years and that’s basically like flipping a coin, 50% chance of not progressing.
So we need something better than that or to improve on it. So we developed a dynamic model and now this is a risk calculator. Any patient, any physician can use the risk calculator and have the prediction of five years, 10 years, 20 years, what is my personal risk based on clinical markers. It doesn’t give you the underlying biology, how fast are they growing. So we need more.
And that the dynamic model helps you because the more data you enter in the light chain increase or the M spike increase, it gives you the dynamics of tumor progression. But we need something as the genomics and immune and other factors. So here’s one of the first papers we published a few years ago where we looked at whole exome sequencing in 250 patients with smoldering myeloma. And now we expanded it of course and we found that there were three main
mechanisms of genomic aberrations. That leads to progression or that are associated strongly with progression to myeloma and these were MAP kinase mutations like ANRAS and Karas ATM and ATR and P53 mutations DNA repair pathway and of course make alterations or translocations. In fact I think that if we have Mike, we already have myeloma and potentially some of those alterations are all secondary mutations and secondary alterations that occur when you’re already going towards myeloma, when there is no coming back and hopefully these.
Will become routine in our understanding of if someone has smoldering myeloma and has one of those likely they have very high risk of progression and we should consider therapeutic interventions in them. Now what we found lately is that one, many of our patients don’t get bone marrow biopsies or serial bone marrow biopsies and two, whole exome sequencing is OK and it’s not good enough because it doesn’t give you the primary events, the translocations that occur in those patients. So this is a paper that.
Just got published a few weeks ago.

Work from Ankit and John Batiste

where we took circulating tumor cells, isolated them, developed a method of low input DNA and were able to do whole genome sequencing from as low as 30 to 50 cells that you can get in the peripheral blood. So you can see in mgs and smoldering myeloma. Many of them have small numbers of circulating tumor cells and when you are able to capture them and purify them, you can do whole genome sequencing and you don't even have to go deep sequencing because the.
Security is so good in those samples. So indeed we had head-to-head comparison of circulating tumor cells versus bone marrow cells so that you can show indeed that all of the clonal and subclonal events can also happen in the blood. And you don't need the bone marrow biopsy, but also head-to-head comparison to fish, which is the standard of care that we have right now in myeloma, yet another 50 year old technology. So indeed, of course, no surprise there that whole genome sequencing is better than fish,
Indeed it. And get you all of the translocations, but it can get you much more. You get mutations, you get copy number alterations, you can even get translocations you couldn’t detect by fish. And indeed because you’re purifying small numbers of cells especially in the peripheral bloods, you can do that multiple times during the serial development of a patients progression. So you can ask the question when the MIC clone is growing, what is going on and when can I treat this patient.
Now I’ll move on to single cell and I borrowed this slide from Aviva. Who basically tries to tell you why do we need to go to the single cell level, and it’s basically when you do bulk sequencing, whether it’s whole genome sequencing or bulk RNA sequencing, you’re sequencing all of the cells mushed together like a smoothie. Now it tastes good, but you can’t really tell the differences between a strawberry and a Raspberry. You can’t even tell if it’s a good Raspberry versus a mutant Raspberry.
Single cell sequencing gives you that. It gives you that ability to differentiate them from each other. And of course spatial transcriptomics or spatial sequencing. Is the ultimate goal where you get the whole fruit tart and you can understand better the localization of all of those cells in the environment. So what we did is we said, let’s look at the tumor cells in the bone marrow compartment. And this is a study where we did it in collaboration with MIT and of course with the broad.
All of our work is with the Broad Institute where we said we're lucky enough in mgus and smoldering myeloma. Not all of the plasma cells are actually malignant plasma cells. So the potential here is instead of looking at interpatient variability, healthy versus cancer patients, we can actually look at the intra patient variability, healthy cells, plasma cells within one patient versus malignant plasma. And now you can ask the
00:27:44.354 --> 00:27:45.853 questions of here are the normal
NOTE Confidence: 0.791874297272727
00:27:45.853 --> 00:27:47.575 plasma cells here are the malignant
NOTE Confidence: 0.791874297272727
00:27:47.575 --> 00:27:49.267 plasma cells from the same patient,
NOTE Confidence: 0.791874297272727
00:27:49.270 --> 00:27:51.433 what are the differences in them and
NOTE Confidence: 0.791874297272727
00:27:51.433 --> 00:27:54.070 can I understand that mechanism of early
NOTE Confidence: 0.791874297272727
00:27:54.070 --> 00:27:55.722 genomic events and transcriptional
NOTE Confidence: 0.791874297272727
00:27:55.722 --> 00:27:57.840 changes that occur with malignant?
NOTE Confidence: 0.791874297272727
00:27:57.840 --> 00:27:58.370 Transformation,
NOTE Confidence: 0.791874297272727
00:28:01.550 --> 00:28:03.278 I can find subclusters that are
NOTE Confidence: 0.791874297272727
00:28:03.278 --> 00:28:04.790 very different from each other.
NOTE Confidence: 0.791874297272727
00:28:04.790 --> 00:28:06.610 There is a proliferating cluster.
NOTE Confidence: 0.791874297272727
00:28:06.610 --> 00:28:08.647 There is some that have higher expression
NOTE Confidence: 0.791874297272727
00:28:08.647 --> 00:28:10.885 of certain genes and that can help you
NOTE Confidence: 0.791874297272727
00:28:10.885 --> 00:28:12.650 understand when the patient is treated,
NOTE Confidence: 0.791874297272727
00:28:12.650 --> 00:28:14.720 which subcluster may respond and which
one may be resistant to therapy.

Now we moved on to do even more work on that.

So this was presented in Ash this year where we showed 245 samples from 234 patients.

Here we did not only do the jacks. The gene expression single cell sequencing, but we also did BCR profiling on all of those patients.

So now you can get with the VGA or with the BCR sequencing the clonality of those patients.

So this just shows you the potential of really understanding the tumor compartment in those patients.
We've done the same thing on circulating tumor cells, but I'm not showing that data here. So of course with a huge number of samples, what was very interesting is indeed all of the malignant samples cluster separately. It was not surprising. We saw that before and the normal plasma cells clustered together from all of the patients and indeed the more you look at the number of cells are increasing as you go on to myeloma, the malignant versus normal compartment. But what was interesting is we compared head-to-head cytogenetics from those patients with fish or when...
00:29:17.099 --> 00:29:18.994 we have whole genome sequencing to
00:29:18.994 --> 00:29:21.034 the single cell RNA sequencing data.
00:29:21.040 --> 00:29:23.352 And indeed you can see that the hyper
00:29:23.352 --> 00:29:25.454 deployed cases were confirmed, the 414,
00:29:25.454 --> 00:29:28.132 you can confirm it with FGFR 311,
00:29:28.132 --> 00:29:30.806 fourteen with cycling. 11416 and so on.
00:29:30.806 --> 00:29:32.844 So you can be very accurate in
00:29:32.844 --> 00:29:34.949 understanding who has a specific
00:29:34.949 --> 00:29:35.370 translocation.
00:29:35.370 --> 00:29:39.296 But then we said well 50% of our samples
00:29:39.296 --> 00:29:41.970 did not even have good fish information.
00:29:41.970 --> 00:29:44.682 Either it failed which happens a lot or
00:29:44.682 --> 00:29:47.201 they give us the fish information with
00:29:47.201 --> 00:29:50.010 an igh partner that we cannot detect.
00:29:50.010 --> 00:29:51.650 So we were basically blinded
to know what is happening.

So we used our single cell RNA sequencing to generate what could potentially be the Cytogenetic information of those patients. So you can see here that all of the unavailable or we didn’t know what they were, we were able to reclassify them into specific cytogenetic abnormalities. And this is the confusion matrix showing you that indeed all of the unclassified we were able to get them into a 4141114 and so on. Biggest number was the hyper deployed numbers. So that can tell you that you can use RNA sequencing to basically
predict what are the cytogenetic abnormalities at the single cell level.

So now you can really say Subclusters of those patients and subclonal abnormalities and we took it even more because we have potentially the ability to identify rare events.

You can now find 814 translocation extremely rare in myeloma. We miss it in many patients and now we can find it with this math A and you can even look at their expression of certain genes.

So for example they express high levels of Mike,
they don’t express other levels of other genes for example in 14.

16 or in 1420 translocations.

So now you can really go into the genetics and the transcriptional changes that are occurring in those rare events.

So when you go back to also looking at the normal versus malignant cells in those patients,

you can also ask questions that are very specific to the phenotype of those patients.

we always think that CD 56 is highly expressed on malignant plasma cells.

That’s not actually true for the small numbers of 1416 and 14.
20 cells, they are negative for CD 56
So now you can really say if I’m going to develop a therapeutic target not BCMA,
but others, I want to understand whether it’s highly expressed on those cells with certain genetic abnormalities and those are the patients that I will not or I will include in my clinical trial. Now moving on to the gene expression data, you can see here these are the top highly expressed or the top. Significantly downregulated genes
across the spectrum from mgus to smoldering myeloma to myeloma.
And because again we have huge numbers of cells, you have more, you have a better ability to detect genes that really are modulated as you go on to progress like. T3 which is a leukemia growth factor as well as transcriptional factor as well as many other genes that get down regulated as you progress but also you can identify new targets potentially for developing therapeutics or new by specifics or new cartes. And then we developed a signature.
that was developed not from the normal plasma cells but from the malignant plasma cells and it was increasing as you go on from mgus to myeloma.

And that signature by NMF by non matrix factorization was able to also detect when we applied it to compass data which is the overt myeloma data, it showed us a progression free survival and overall survival difference and it could be predictive of prognostic risk in those patients. So if you put that.

In those patients as well as looking at the proliferation index,
you can actually stratify the patients as low risk, intermediate and high risk even in the compass data in those patients. We then applied it to the gene expression data to all gene expression data from mgus to myeloma and indeed show that this can be predictive. So again not only genomics like DNA data that we have. Like map kinase mutations and so on can be predictive of who will progress. Now at the RNA level, we also have a gene expression profile that can be predictive of who would progress and who will not.
So moving on to the immune system, here I'm showing you that the tumor system is an ecosystem. You cannot look only at the cancer cells, you need to look at the cancer and immune cells and of course not immune cells to understand better what causes progression. So the first thing we did a few years ago is again we did single cell sequencing. Of the immune cells in the bone marrow from MGUS smoldering to myeloma. And indeed what was surprising is we found that there were compositional changes that happened as early as MGUS.
And we were shocked because we usually think that MGUS is a benign disease. You’re walking around, you have a very small chance of progression. Why would your immune system be so altered that it looks like myeloma? We found Tregs are increased, monocytes are increased, NK cells are altered, and then later on you have further functional changes. You have loss of the memory cytotoxic CD8 cells and then you start having less granzyme K which are the earlier stem cells and more granzyme B in those patients. And this is just showing you...
00:34:35.480 --> 00:34:36.260 some of those changes.

00:34:36.260 --> 00:34:38.801 You can see here those memory excitotoxic

00:34:38.801 --> 00:34:40.918 cells almost completely depleted in

00:34:40.918 --> 00:34:42.666 patients with smoldering myeloma,

00:34:42.670 --> 00:34:43.730 sorry, with overt myeloma.

00:34:43.730 --> 00:34:46.018 So we went on to ask a couple

00:34:46.018 --> 00:34:46.966 of other questions.

00:34:46.970 --> 00:34:47.568 One is,

00:34:47.568 --> 00:34:49.661 are those changes altered if I treat

00:34:49.661 --> 00:34:50.950 someone with smoldering myeloma

00:34:50.950 --> 00:34:53.560 and can we expand that in also the

00:34:53.560 --> 00:34:55.430 peripheral blood of those patients?

00:34:55.430 --> 00:34:57.590 So this is work by Romanos,

00:34:57.590 --> 00:35:03.020 just got published a couple of weeks ago,
samples from patients on a clinical trial.
With Elotuzumab limited dexamethasone
patients who were treated on high risk
smoldering trial and we took samples
baseline cycle nine and end of therapy.
And what we found is we
found a couple of things.
First is of course,
the compositional changes were very similar
to what you expected in our other study,
but now it’s a much bigger #190 samples.
So indeed more T regs,
more CD4 TNS and so on.
But what we found that was
interesting is a couple of things.
One,
because we had single cell TCR sequencing on all of those patients, we found that you actually have a significant change in the diversity of the T cells even in early smoldering myeloma. So this is just showing you when I resample the TCR in all of those patients, always we had a smaller diversity in the healthy compared to smoldering myeloma. So it shrinks significantly and you would think that it shrinks because you have one clone that expands. So the diversity is smaller and indeed, it is clonal expansion.
but it’s not just one clone, it’s multiple clones and some of them are very small clones that expand in those patients. Now, interestingly, that expansion was merely in granzyme BC8T cells. As well as T regs, and you can see it here, uh, nicely that those clonal T cell expansions were in the CD 8 terms in those patients. So that tells you the immune system is trying to react to the cancer cells, but it’s exhaustive and it cannot do a very good job in responding to those cancer cells and that could potentially be useful for therapeutic
interventions in the future, especially with TCR therapeutics as we go on. Now, the other question we said is can we use the immune system as a biomarker? Of disease progression, can I use an immune signature that tells me this patient will respond to therapy or not? And after therapy did they normalize their immune system. So indeed we found the signature that is predictive of response which is if you are reactive to the tumor cells then you have a better chance of responding to therapy and a
long-term progression free survival.

And post therapy if you normalize your immune system indeed you have a much better progression free survival and that tells us that indeed those patients can have that normalization of the immune system along with MRD and we're hoping to apply that for all of the future studies so that you don't only look for Mart, you also look for pin in those patients and this is just showing you some of those factors specifically for grand time, as you go on to that normalization.
in those patients, now we moved on into the blood and said, can we use the blood instead of the bone marrow again in those patients. So indeed here is just showing you the volcano plot of those patients and indeed you have the same changes in the blood as you have in the bone marrow of those patients and the same thing also happens for the T cell receptor. So this is just showing you the T cell diversity and the peripheral blood. And it mimicked exactly what happens in the bone marrow of those patients. Not only that,
if I just do another confusion plot and say give me randomly anyone who has a peripheral blood sample and I will tell you if they have mgus or not. It was very predictive in the blood by the immune cell signature that I can tell you this one is healthy, this one is mgus. Now that opened the door for us to say can we use it also for cancer screening in general. And this is something that we’re trying to develop right now.
which means that we have 317 new samples
that we sequenced bone marrow and
peripheral blood to really ask those
bigger questions of immune regulation
in mgus and smoldering myeloma.
And now you can have more
expression data that really
defines the progression signatures
because you have more samples,
you can differentiate what causes progression
from mgus to smoldering to myeloma,
not causes what is associated with it.
Hopefully causative would be all
of the functional studies that we.
Can do in vivo and in vitro to say
what is really causing progression in those patients and then of course at the gene expression level. So at the compositional changes, most of the things happen at mgus and then they stay constant or increased slightly. But at the signatures of the genes you have a huge difference in interference signaling. You see that sudden change of granzyme B increasing and you have more of those granzyme BCZ its cells that are more senescent as you can see with their expression of KR. One and less cytolytic. So they’re not capable of really responding to the cancer cells.
and this is just showing you how altered immune system goes on from progression from mgus to myeloma. And then again because we have so many samples, especially low risk smoldering, which we think is likely more like an mgus and some of those mgus look more like smoldering myeloma. So the clinical factors of what we call mgus and what we call smoldering myeloma may actually be biologically completely different. And they are intermixed with mgus and smoldering myeloma.
We have biological relevance from each other. So you can see here huge diversity changes that occur in some of the MGA samples as well as the smoldering myeloma samples in those populations. And then finally, we’re starting to look at the spatial transcriptomics. But until then we started to look at the cells that basically are adhered to each other. But until then we started to look at the cells that basically are adhered to each other. What is close to a myeloma cell when we pull it in a CD130 is selection, and indeed we found many of the. Megakaryocytes were highly, B cells, granzyme key positive cells and.
uh, you know, attached to the tumor cells indicating that there is a lot of interaction between those cells. So in the last few minutes I'll talk about clinical interception and we have done many clinical trials throughout the years, but now we're thinking of it more precise in our interception what we call precision interception. So in the older days we have shown there is a proof of concept.
Observation versus treatment is better. In progression free survival and one case overall survival with the Lenalidomide index studies. But these were early events or early attempts. Let’s do something better than that. So our efforts are divided into early prevention, metformin, intermittent fasting, things that really prevent progression. Then we have targeted approaches, MAP kinase mutations, with venetoclax, we’re looking at synthetically salty in one queue,
abnormalities and so on.

Then we have Immunotherapeutics, vaccines, T cell therapy with carton by specifics and so on, and then novel combinations.

And we’re doing now 4 drug regimen. There are RVD, which is basically the standard of care of myeloma. Bringing it on into an earlier setting with the idea that can we cure the patients at the earlier precursor stages and at least can we make sure that we do never develop end organ damage in those patients.
So I’ll just give you a couple of examples of those trials. This one is ongoing right now, immunol prism and this is the first time we treat patients with immunotherapy in smoldering myeloma. So we chose these inclusion criteria for high risk smoldering myeloma and we’re randomizing patients 2 to one to tech listenable. Bcma CD3 antibody by specific antibody or landex, our first six patients were only to Christmas because the FDA mandated that we go very slowly and we do lose reduction. And then now we’re actually
randomizing patients and we're up to
18 patients currently either treated
or going to treat soon with the
primary endpoint of response rate.
And I can tell you preliminary,
we are not seeing the same rate of CRS.
We are not seeing the same rate
of infections you see in other
patients and we're seeing impressive
responses in those patients.
And then of course the other option
is can I use the one and done cartee
therapy as early as possible when
you have less tumor burden and when
you have better T cell response.
and potentially will this be a curative intent in our patients. So we’re hoping to open soon the first car T therapy in early precursor settings in high risk smoldering myeloma. And I can tell you when I submitted it to the FDA, the first thing I got back was absolutely not, you’re not doing this and we were able to convince the FDA to give us the Ind. And we’re hoping soon to open that trial. So with that, I hope I convince you that early detection and early interception in one disease like myeloma matters.
And hopefully this can be applied to many other diseases and we can change the survival of our patients. 

And I want to thank of course amazing people, the lab, the clinical teams, our collaborators from really all over the world, but all of course our funders. 

And just basically does everything with us at the Broad Institute and above all our patients. Thank you.
I mean, absolutely spectacular, incredibly exciting. So we have Doctor Nefarious here as our panelist too. And maybe I have a quick question. Do you see correlations between the mutational spectrum and the immune environment? Yeah. How do they happen? Yeah, we haven’t even started putting it together. I mean it’s it’s an so if any bioinformaticians you have, please come because we have enough data for many years to analyze the data. But yes, now that we have that many samples,
00:44:46.120 --> 00:44:47.884 you can start asking the question
NOTE Confidence: 0.946640661666667
00:44:47.884 --> 00:44:50.499 in an 1114 or in a certain mutation,
NOTE Confidence: 0.946640661666667
00:44:50.500 --> 00:44:52.156 what are the immune, that’s regulations.
NOTE Confidence: 0.946640661666667
00:44:52.160 --> 00:44:54.029 The older samples were very small numbers
NOTE Confidence: 0.946640661666667
00:44:54.029 --> 00:44:56.100 and of course if you start subdividing,
NOTE Confidence: 0.946640661666667
00:44:56.100 --> 00:44:58.718 if P53 haven’t foreseen, you don’t have.
NOTE Confidence: 0.946640661666667
00:44:58.720 --> 00:44:59.450 Of data.
NOTE Confidence: 0.946640661666667
00:44:59.450 --> 00:45:02.005 But now as we’re enlarging the cohorts,
NOTE Confidence: 0.946640661666667
00:45:02.010 --> 00:45:04.110 we will start to see that correlation.
NOTE Confidence: 0.11864579
00:45:09.990 --> 00:45:11.240 Now you wanna ask a question,
NOTE Confidence: 0.767392458
00:45:11.250 --> 00:45:12.674 I think there there is a question in
NOTE Confidence: 0.767392458
00:45:12.674 --> 00:45:14.539 the chat, but Irene congratulations
NOTE Confidence: 0.767392458
00:45:14.539 --> 00:45:17.054 on your really tremendous success
NOTE Confidence: 0.767392458
00:45:17.054 --> 00:45:19.889 and in terms of promise study,
NOTE Confidence: 0.767392458
00:45:19.890 --> 00:45:23.026 I think that’s really a successful enrollment
NOTE Confidence: 0.767392458
and of extensive data generated there.

In terms of potential future clinical applications,

I mean terms like number needed to screen are used for breast cancer,

80 or 100 seems acceptable.

What’s your sense of number needed to screen potentially for high risk patients with myeloma?

Or perhaps those with family history.

Yeah,

great question. And this is indeed exactly the question of how can we make it standard of care,
I think unlike breast cancer and other solid tumors where you know that if you cut it and the patient survived in mgus, if you find it, what is the relevance, right, because we know sensitivity and specificity is very good. So that's not the problem that we have. So I think what we have thought of is actually. That showed that indeed interception matters because then early detection would matter and 13% prevalence is a huge number. I mean these are not numbers you
00:46:18.951 --> 00:46:20.209 see in any other cancer right,

NOTE Confidence: 0.907051688333333

00:46:20.210 --> 00:46:21.988 breast or lung and all of those.

NOTE Confidence: 0.907051688333333

00:46:21.990 --> 00:46:24.580 So a high risk population being African

NOTE Confidence: 0.907051688333333

00:46:24.580 --> 00:46:27.101 American or of African descent or

NOTE Confidence: 0.907051688333333

00:46:27.101 --> 00:46:28.967 black or first degree family members

NOTE Confidence: 0.907051688333333

00:46:28.967 --> 00:46:31.110 should be such a low hanging fruit.

NOTE Confidence: 0.907051688333333

00:46:31.110 --> 00:46:33.644 Like you don’t need to justify numbers

NOTE Confidence: 0.907051688333333

00:46:33.644 --> 00:46:35.926 needed to treat with the 13% prevalence.

NOTE Confidence: 0.907051688333333

00:46:35.926 --> 00:46:38.770 And that’s just mgus if you add the M

NOTE Confidence: 0.907051688333333

00:46:38.836 --> 00:46:40.896 *** which could be the taxing lymphomas.

NOTE Confidence: 0.907051688333333

00:46:40.900 --> 00:46:42.622 Now we have a huge number of

NOTE Confidence: 0.907051688333333

00:46:42.622 --> 00:46:44.084 people walking around with early

NOTE Confidence: 0.907051688333333

00:46:44.084 --> 00:46:45.089 lymphomas and myelomas.

NOTE Confidence: 0.8786183

00:46:45.520 --> 00:46:49.550 And if I, if I may just ask one more in terms

NOTE Confidence: 0.885824233125

00:46:49.625 --> 00:46:51.215 of I think you put you,

NOTE Confidence: 0.885824233125

00:46:51.220 --> 00:46:53.173 you had some of this in the slides in
00:46:53.173 --> 00:46:55.452 terms of you know fasting or metformin
00:46:55.452 --> 00:46:56.788 or other metabolic interventions.
00:46:56.790 --> 00:46:58.720 What’s your potential vision on
00:47:00.710 --> 00:47:02.670 you capture as mgus or early stage?
00:47:02.670 --> 00:47:03.966 What’s your current counseling
00:47:03.966 --> 00:47:05.450 that you provide? Yeah,
00:47:05.460 --> 00:47:07.134 so you know the interceptions are
00:47:07.134 --> 00:47:08.867 easy because I can give something
00:47:08.867 --> 00:47:10.553 and I can see the response.
00:47:10.560 --> 00:47:12.877 But then so many patients have this
00:47:12.877 --> 00:47:15.043 earlier factors and there’s a lot
00:47:15.043 --> 00:47:16.888 of questions of obesity microbiome.
00:47:16.890 --> 00:47:18.820 Metabolic pathways, so we’re starting
00:47:18.820 --> 00:47:20.750 to do now microbiome studies.
We’re starting to do metabolic changes and immune and again they come together, right, the microbiome, the metabolomics and the immune dysregulation to lead to progression. So a lot of that effort we’re starting to work on because that can also be therapeutically intervened with whether you have microbiome therapy or of course other mechanisms. And then Catherine Mayernik and Betsy O’Donnell are amazing and trying to develop other studies like that metformin, intermittent fasting. Exercise and fitness things that can really help modulate the lifestyle of
patients for modifications basically that can help prevent progression.

Yeah, I think your former answer may have to Natalia may have answered the question in the chat um by um Manju Prasad who’s asking is risk stratification for mgas being offered to patients in the clinical setting.

Yeah. So actually our publication that just came out yesterday and Nancy mythology was specifically to ask that question because many of our patients don’t have a bone marrow biopsy.

So you think they have mgus, they actually have smoldering myeloma and
then you don’t even know and as I said the.

Clinical annotation of what is mgus

and what smoldering myeloma is so

hard because the bone marrow is patchy.

So I can have a 10% plasma cells

but I’m really mgus or I’m not

really small ring myeloma. So the

Pangea model was actually

6700 participants where we annotated

all of their clinical data and we

developed the clinical model of

progression based on dynamic numbers.

If they’re M spike is increasing,

If their light chains chain is

increasing hemoglobin it would freezing,

creatinine is increasing.
00:48:56.479 --> 00:48:58.477 Remember all of those are blood
00:48:58.477 --> 00:49:00.427 things and then we added bone marrow,
00:49:00.430 --> 00:49:02.347 uh, as well as age and we did the
00:49:02.347 --> 00:49:04.074 model with or without bone marrow
00:49:04.074 --> 00:49:05.818 biopsy to help you really say
00:49:05.818 --> 00:49:07.449 if I had a bone marrow biopsy,
00:49:07.450 --> 00:49:08.002 here’s the risk,
00:49:08.002 --> 00:49:09.490 if I don’t have the bone marrow box,
00:49:09.490 --> 00:49:10.348 here’s the risk.
00:49:10.348 --> 00:49:13.205 But it was a model for all small ring model.
00:49:13.205 --> 00:49:14.630 So I would use it.
00:49:14.630 --> 00:49:16.550 It’s available online there is calculated.
00:49:16.550 --> 00:49:18.170 So look up angia and hopefully
00:49:18.170 --> 00:49:19.590 you’ll be able to find.
00:49:21.880 --> 00:49:25.640 Other conflicts? And considering the
00:49:25.640 --> 00:49:28.880
00:49:25.640 --> 00:49:27.880 fact that so many of these younger
NOTE Confidence: 0.13883433
00:49:27.945 --> 00:49:30.045 patients who are diagnosed with full
NOTE Confidence: 0.13883433
00:49:30.045 --> 00:49:32.158 blown myeloma in their 30s or 40s,
NOTE Confidence: 0.13883433
00:49:32.160 --> 00:49:34.648 you’d have to conceive that there are likely
NOTE Confidence: 0.13883433
00:49:34.648 --> 00:49:37.217 have had endust from their teenage years.
NOTE Confidence: 0.13883433
00:49:37.220 --> 00:49:40.541 So I wonder if you have any germ line
NOTE Confidence: 0.13883433
00:49:40.541 --> 00:49:43.510 genomic data within the within the
NOTE Confidence: 0.13883433
00:49:43.510 --> 00:49:45.821 promise cohort or elsewhere? Yeah.
NOTE Confidence: 0.13883433
00:49:45.821 --> 00:49:48.530 So we are trying to sequence right now all
NOTE Confidence: 0.13883433
00:49:48.598 --> 00:49:51.300 of the samples which won’t even sequencing.
NOTE Confidence: 0.13883433
00:49:51.300 --> 00:49:54.867 Uh, the MGB cohort already had their
NOTE Confidence: 0.13883433
00:49:54.867 --> 00:49:57.069 smooth arrays or now they’re actually
NOTE Confidence: 0.13883433
00:49:57.069 --> 00:49:59.147 redoing whole thing security in the
NOTE Confidence: 0.13883433
00:49:59.147 --> 00:50:01.268 same samples and then of course many
NOTE Confidence: 0.13883433
00:50:01.333 --> 00:50:03.259 of those other folks had already.
NOTE Confidence: 0.13883433
00:50:03.260 --> 00:50:05.018 So you’re right, we’re trying to
actually do that all of this data.

OK, I think they’re having some static from me or from somewhere else.

Nope, it’s. OK, it may have been your computer, but let me umm,

So there this Mendez

So how do you think of

mgip compared to lymphoid,

clonal hematopoiesis and is in GIMP

and the absence of lymphoma CL and

manifestation of lymphoid cloning,

hematopoiesis and then any information

on overlapping somatic mutations.

So great question. So we work very
closely with Ben Ebert and Lachelle

weeks and others to understand really

the interlink between Chip and.

Mgus and we are, as we speak,

trying to sequence all our samples for that.

It’s hard to know whether there is

an overlap of the mutations or not.

I think we need to 1st see how many of them

do have chip and then we try to understand.

We worked with Dan Lando where we took

some of our chip samples from myeloma and

we did the single cell sequencing data,

but most of the chip mutations were

in the myeloid lineage and not

in the lymphoid lineage.

But that brings up the
lymphoid chip question.
And again until we have more data we don’t know the answer but it’s a great question.
We have another question from American Idol and I think this highlights how important is it is that we think mechanism and disease agnostic and across specialties. So Amir is of course loving you talk.
And then right we have similar similar issues in chips because MB spectrum in terms of difficulties of response assessment. And So what do you think the primary endpoint of early phase trial for high risk
00:51:50.420 --> 00:51:52.284 smoldering myeloma should be the great?
NOTE Confidence: 0.752938765714286
00:51:52.284 --> 00:51:53.594 Question, because if we wait
NOTE Confidence: 0.752938765714286
00:51:53.594 --> 00:51:54.860 for progression to myeloma,
NOTE Confidence: 0.752938765714286
00:51:54.860 --> 00:51:56.712 especially if you treat them in the
NOTE Confidence: 0.752938765714286
00:51:56.712 --> 00:51:58.060 observation arm with Rev depth,
NOTE Confidence: 0.752938765714286
00:51:58.060 --> 00:52:00.970 you’re wait for another 1520 years.
NOTE Confidence: 0.752938765714286
00:52:00.970 --> 00:52:03.085 So we do have a meeting with the FDA,
NOTE Confidence: 0.752938765714286
00:52:03.090 --> 00:52:05.941 which actually is in Madrid to ask those
NOTE Confidence: 0.752938765714286
00:52:05.941 --> 00:52:07.326 questions. What are the endpoints?
NOTE Confidence: 0.752938765714286
00:52:07.330 --> 00:52:08.980 Can we get accelerated endpoints?
NOTE Confidence: 0.752938765714286
00:52:08.980 --> 00:52:12.050 Can we look at response, can we look at RT?
NOTE Confidence: 0.752938765714286
00:52:12.050 --> 00:52:14.802 Can we consider pure as a sustained MRD
NOTE Confidence: 0.752938765714286
00:52:14.802 --> 00:52:16.970 negative disease for four to five years?
NOTE Confidence: 0.752938765714286
00:52:16.970 --> 00:52:18.728 These are all great questions that
NOTE Confidence: 0.752938765714286
00:52:18.728 --> 00:52:21.104 we need answers to be able to design
NOTE Confidence: 0.752938765714286
00:52:21.104 --> 00:52:22.167 for this property. Yes.

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Let me maybe go back then to the interplay between the immune system and your clone. So do you expect that if you get rid of the malignant clone, however small, that it would have an effect on the immune system? Oh, I don’t know. That’s a great question. Will it normalize, right? I mean, if you look at the therapy we gave to those patients and when they were MRD negative, they normalized their immune system. But the other question is
which one started first?

Is it the chicken and the egg?

And was it already an immune dysregulation that led to those clones?

Growing.

And is that already there even when you get rid of the MRI of the clone that years and years later yet another mutation will occur because the soil is fertile, right? So I don’t know.

And I’d love to get samples, for example, from patients before they develop mgus so that we know which one happens first.
But these are all great questions that we would love to collaborate with people and answer them together.

Awesome. We have a little more Natalia. Any questions from your team?

Yeah, I mean, I think, uh, perhaps, uh, to answer amers question and perhaps a, an immune endpoint should be a potential secondary endpoint, how to normalize that immunosuppressive environment, you know what potential interventional strategies like whether it’s nutritional or microbiome or metabolomic strategies that could be,
I don’t think we pay enough attention to weight loss interventions or exercise interventions in myeloma and there’s so much. Data you made parallels Irene with breast cancer and there’s so much commonality between the diseases, the role of inflammation, the obesity etcetera. So I don’t think we pay enough attention to those kind of interventions in myeloma prevention and even relapse prevention once you have successfully treated them. Absolutely. And I think you and Betsy
O'Donnell would really, you know, talk for hours because we’re even thinking should we use some of those new obesity drugs, right? Like, there are so many things that we can do to prevent progression and some of them may be in our hands right now.

Yeah, excellent. So we’re getting close to running clock and I don’t see additional questions. Um, well, I’m Erin, thank you so much for this really spectacular grand rounds and congratulations on these amazing advances that are clearly, you know,
advancing prevention which is so amazing

for many patients and then treatment.

So thank you. Thank you for sticking through you know with the zoom only option.

And we look forward to you know, getting together in person and collaborating for sure.

Absolutely. Thank you again and definitely look forward to seeing you.

Not in person, but this was a good alternative. Fantastic

talk, Harry. Thank you so much.

Thank you, everyone.