All right, everyone.

We’re going to go ahead and get started again and continue on.

And it is my pleasure to introduce our next speaker who like all of our speakers today, really doesn’t need an introduction.

Dr. Krumholtz graduated from Yale College and earned his medical degree from Harvard Medical School.

He completed internship and residency programs in medicine at the University of California, San Francisco, and did a fellowship in cardiovascular
00:00:28.048 --> 00:00:30.080 medicine at Beth Israel in Boston.
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00:00:30.080 --> 00:00:32.607 And he earned a master’s degree at
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00:00:32.607 --> 00:00:35.364 Harvard School of Public Health in 1995.
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00:00:35.364 --> 00:00:39.236 In 1995, in his third year at year,
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00:00:39.240 --> 00:00:41.640 he founded the Center for
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00:00:41.640 --> 00:00:43.560 Outcomes Research and Evaluation,
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00:00:43.560 --> 00:00:46.850 and in 2005, he was named the
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00:00:46.850 --> 00:00:49.320 Harold Hines Junior Professor.
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00:00:49.320 --> 00:00:52.036 Yeah, I have to follow the script.
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00:00:52.040 --> 00:00:53.200 OK Was that my
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00:00:53.240 --> 00:00:53.804 phone or yours?
NOTE Confidence: 0.752049021428571

00:00:53.804 --> 00:00:56.640 OK, good. Cool. Great job.
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00:00:56.640 --> 00:00:57.558 Wow, what a pleasure to be
NOTE Confidence: 0.752049021428571

00:00:57.558 --> 00:00:58.520 able to speak with you guys.
NOTE Confidence: 0.752049021428571

00:00:58.520 --> 00:01:00.200 And what an amazing Dean’s workshop.
Thank you to Dean Brown for
setting this up and for Anya,
one of my heroes and is doing such
a great job in the era of OBESI.
I think the leading,
the internationally leading
figure in obesity medicine today,
both because of the quality of her science,
the strength of her voice,
and her ability to inspire
all those around her.
But she really is worth.
We are fortunate to have her here. So my
OK disclosures.
So there’s AI would say fledgling
team of outcomes researchers.

And I’m going to recruit you all to join us, but at the center to really support Anya’s vision about how we’re at a central juncture in the treatment of obesity in this country and around the world with tools that are emerging at a dizzying pace, putting us in a position to do things that were unimaginable even five years ago. So the question will be will the evidence generation keep pace with our needs to help this in this transformation. And again, you know, Anya, I think is at the center of this, but Rohan, Keira, you and Lou, Erica,
Spatz and many others, Mona Sharifi, others I should have put on this slide who are doing important work in this area and I think we’re gonna grow is a facet of what Y weight is about, a facet of this work. So what is outcomes research? Many of you may not be familiar with this. I think it’s a more of a basic science orientation. So it’s really science that concerns itself with the result. We sort of say the end result, what are we really achieving at the end of the day?
How do we tangibly affect people’s lives?

What can we do to improve their outcomes?

Not just about declaring victory because we’ve had a paper or there’s a breakthrough or there’s a new study,

but at the end of the day, have we really affected population?

So what should we do exactly?

And not only the what, but how should we do it in ways that we know we can actually ensure, that this is being adopted broadly and appropriately monitoring that adoption and ensuring again that individuals are benefiting.
And we'll be focused on in this kind of research on effectiveness, efficiency, equity, patient centeredness, safety and timeliness. So you know, what's the moment? Obesity is endemic and it's causing much suffering and cost. And by the way, because suffering and cost means there's the prospect that actually treating it will lead to economic incentives and motivations 'cause sometimes we have innovations that can be beneficial to people, but there's not an economic reason for the healthcare system to reorient.
But as we go to value based cares, people have become increasingly interested in population health. There's a strong motivation here. And let me just say clearly and of course, Anya is a great influence of for me on this, but really obesity treatment's not about appearance, but it’s about health. And I think it’s the idea that we've got these medications to treat obesity and reduce risk. I sort of think about the weight loss tongue in cheek as a side effect. Actually, it’s a really good side effect.
because it helps us with compliance.

People actually like this side effect.

So they’re going to continue

But as physicians,

our central drive is to improve health

and reduce risk, advance global health.

And I think This is why we’re

And I think it’s a historic juncture.

So you may have seen this,

this graphic and others.

This week Lancet came out with a sort

of landmark non communicable disease

groups publication on obesity worldwide.
This is kind of a cool figure. I just like the way it looks. I don’t know what it means, but I’m just joking. But the it’s 1990 on the left side in in 2022 on the right side for every country in the world. And if you look at the red, you know there’s some percentages of people with obesity and you can see what’s happening. I could have shown you figures from throughout this article. It shows what you already know that there’s been a great degree of growth.
so we’re making such progress in cardiovascular disease for decades. It’s slowed. In 2022, CDC reported that we actually had an uptick in cardiovascular mortality. I attributed it to this decade long, decades long increase in obesity that’s coming to roost now. And we were really only treating sort of the manifestations, lipids and blood pressure, but not getting to the root cause that many people, which was the obesity itself.
This is what’s changing. This is again showing 1990 to 2022 across the world. It doesn’t show any surprise. I’m just doing it to emphasize that this is a pressing need. There’s an urgent issue that’s affecting population health throughout the world and now we have ability to treat this. So you know my view is that again to reinforce this, we’ve been treating manifestations of obesity as population health has steadily declined but after after this period of marked improvement.
But we failed on the root cause and most of our arsenal up until now has lacked safety and effectiveness. We now strategies that address obesity and can improve health and like I said, I consider weight loss. But what we have now is evidence and questions. As compelling evidence comes out from Phase 3 clinical trials, it really starts to open up a wider range of questions that are needed if we're to understand how to optimize the use of these new
medications And if we’re able to ensure the proper implementation and application of this new knowledge in ways that will tangibly show by improvements in health.

And so our strategies on the outcomes research side is to answer these questions. And what we’re trying to do is to assemble a range of, you know if they’re people here from the lab, I’ll say these are our reagents, our data reagents in order to do data experiments in order to generate knowledge that will fuel the proper application of these...
new strategies that are going to come out at a dizzying pace. It’s not just the two meds that we have now, it’s going to be 10s, twenty different kinds of medications and choices and we’re going to have to parse this or make challenges around access and cost. They’re going to be a question of who’s best in, and it’s going to be a question of how to optimize it for anyone for whom it is effective. And so we’ll use federal databases and public registries like UK Biobank, clinical trial databases, and international data repositories.
like the Odyssey trials,
prospective decentralized registries,
regulatory science analysis and preview
simulation, decentralized trials.
The thing about outcomes research
is we have a broad toolkit because
we’re motivated by the questions,
not by having a singular approach
we have a broad toolkit because
we’re motivated by the questions,
not by having a singular approach
or type of analysis,
but by being able to approach
us in many different ways.
And I want to say we’ve been
at this for a while.
Rohan had this you know,
00:07:51.440 --> 00:07:52.445 piece in JAMA.
00:07:52.445 --> 00:07:54.120 You’ll see that this we’re,
00:07:54.120 --> 00:07:56.488 this group is not new to the issue
00:07:56.488 --> 00:07:57.080 of obesity.
00:07:57.080 --> 00:07:59.397 This paper actually we’re writing a long
00:07:59.397 --> 00:08:01.839 time ago but after low carbohydrate
00:08:01.840 --> 00:08:04.222 diets and the obesity paradox was
00:08:04.222 --> 00:08:06.322 something we published in Heart
00:08:06.322 --> 00:08:10.792 Body mass index and mortality and
00:08:10.792 --> 00:08:12.360 acute micro infarction patients.
00:08:12.360 --> 00:08:14.028 I do self and parent reported
00:08:14.028 --> 00:08:15.140 dietary physical activity and
00:08:15.187 --> 00:08:16.747 sedentary behaviors predict worsening
00:08:16.747 --> 00:08:17.917 obesity in children.
This was a PhD thesis from someone in investigative medicine, Karen Dorsey, who has focused her thesis on this and applying practice recommendations for prevention and treatment of obesity in children and adolescents. We did this internationally. We looked in China in a million persons project that we designed in order to understand risk within large scale populations in China and we published this in German network about body mass index with blood pressure in 1.7 million Chinese adults.
We were looking at the issues around disparities and barriers to access looking at racial and ethnic disparities and financial barriers and overweight and obese adults eligible for Smeglitide in the US by you and Lou. Another one that you and did with Anya looking at what were the implications for the select trial with regard to the population that might be eligible for it. I’m only just saying this because we’ve been at this for a while.
but now we’ve got a center,
now we’ve got the world’s leading expert in obesity medicine.
I think we’re poised to kind of organize these efforts that have been a little disparate and not necessarily concentrated in a way that really positions Yale as a real leader and as a pillar of what this center is going to be about.
Obviously there’s other science you’ve been discussing today.
There’s a wide range of great science at Yale in this area.
We want outcomes research to have a big according to that.
And I just said what we don’t know is enormous and I was just throwing these downs.

How do we optimize the safety and effects, not just writing the prescription.

What’s different to the people who have success with the prescription versus people who don’t?

How can we understand the context of the lives?

What should we be telling them behaviorally?

How do we set them up for success?

What does it mean between those who succeed in failure?

What are the range and magnitude of benefits?
Who benefits and why?
Who incurs safety issues and why?
Who should we prioritize?
You know these trials, they haven’t included a large number of minoritized populations.
They haven’t includes a large number of elderly populations.
They haven’t included a large number of younger populations.
If people are going to be on this for 10 years, none of them have gone beyond three years so far.
So what happens?
What happens when people stop and start,
what happens when people switch types of medications. These are real world questions that clinicians and their patients are going to need to know if they’re going to be making informed choices. In the end is a cost effective. Can we make the case? Because the benefit, interestingly, in select, when people were treated with some agglutide, the benefit accrued almost immediately before you could discern the weight loss so that the curves continue to depart.
But that benefit was very early.

Can that manifest as a cost saving?

Even people talk about this bankrupting Medicare,

bankrupting the health system,

but maybe it’ll actually turn that on its head because of its health effects,

orthopaedic procedures, cancers,

as well as cardiovascular.

We need to look at all this stuff.

What we’ve got trials, very carefully selected groups that got into well curated and overseen phase three clinical trials.
What happens in the wild, what happens when we’re really out in the world? Who gets access and how does this work now? I wanted to present just a little bit of information at what we’ve been working on recently, which is to try to see how can we get within healthcare systems and be able to get real time feedback on performance and the situation around something like obesity. Now we’ve been working with Centara, an $8 billion healthcare system with about 22 hospitals in Southern Virginia,
Northern North Carolina.

It turns out our relationship with Centara, we have greater access to healthcare data than we do in the Yale system.

We actually have to go. We have to. I'm just had a Crick in my neck but it happens. We have to go elsewhere to be able to get this. We're working hard with Daniela and Lucilla and this will be solved here and we'll soon be in the same position. But but we've been able to work with Centaur. You know it turns out if you just depend on the problem list or the ICD codes or the sort of typical structured field.
within within the the medical record, you can’t quite get this. But we can triangulate on this and start to see for example this is just looking at you know both prescription counts for semaglutide here. We’re looking at the prevalence in Centaur, 41% prevalence of obesity and we’re looking at the use of semaglutide only 2%. You know people talk about this going wild actually number total prescriptions in the country still remain far, far lower in terms of single digit percentages like under 5% for
compared to the number of people who could benefit from this. So but we’re able to show this, we can identify them. By the way, if this is for trial recruitment, immediately we find people, we’re developing the tools so that we can use the raw data within the electronic medical record to move quickly and we can also follow people over time to say this is what they were like in in two periods before. This is by the way you and Lou and the group at Centaur, I really want to shout out you and that you know can say that in in
00:13:27.237 --> 00:13:28.638 sort of the control period before
NOTE Confidence: 0.927160284
00:13:28.638 --> 00:13:30.038 they start on some gluttitis,
NOTE Confidence: 0.927160284
00:13:30.040 --> 00:13:32.028 the -3 negative two period zero and
NOTE Confidence: 0.927160284
00:13:32.028 --> 00:13:34.058 now you can see they’re starting
NOTE Confidence: 0.927160284
00:13:34.058 --> 00:13:36.278 on it and what’s their trajectory.
NOTE Confidence: 0.927160284
00:13:36.280 --> 00:13:39.159 So in the real world what are we
NOTE Confidence: 0.927160284
00:13:39.160 --> 00:13:40.318 observing and who’s benefiting,
NOTE Confidence: 0.927160284
00:13:40.320 --> 00:13:42.462 who’s not, who stays on it,
NOTE Confidence: 0.927160284
00:13:42.462 --> 00:13:43.680 who doesn’t and what kind of health
NOTE Confidence: 0.927160284
00:13:43.680 --> 00:13:45.912 reduction do you see?
NOTE Confidence: 0.927160284
00:13:45.920 --> 00:13:47.544 She was showing this in even larger
NOTE Confidence: 0.927160284
00:13:47.544 --> 00:13:48.240 numbers of periods.
NOTE Confidence: 0.927160284
00:13:48.240 --> 00:13:50.184 And it what’s nice about is when you
NOTE Confidence: 0.927160284
00:13:50.184 --> 00:13:52.119 start even truncating it into periods,
00:13:52.120 --> 00:13:53.535 weight happens to be something
NOTE Confidence: 0.927160284
00:13:53.535 --> 00:13:54.950 that’s very commonly measured within
NOTE Confidence: 0.927160284
00:13:54.998 --> 00:13:55.760 the health record.
NOTE Confidence: 0.927160284
00:13:55.760 --> 00:13:56.744 And we can actually show what
NOTE Confidence: 0.927160284
00:13:56.744 --> 00:13:57.236 we would expect,
NOTE Confidence: 0.927160284
00:13:57.240 --> 00:13:59.040 which is the longer people were on it,
NOTE Confidence: 0.927160284
00:13:59.040 --> 00:13:59.946 the more decline.
NOTE Confidence: 0.927160284
00:13:59.946 --> 00:14:01.758 This is in body mass index.
NOTE Confidence: 0.927160284
00:14:01.760 --> 00:14:02.693 So you know,
NOTE Confidence: 0.927160284
00:14:02.693 --> 00:14:04.914 one body mass index is usually, you know,
NOTE Confidence: 0.927160284
00:14:04.914 --> 00:14:06.153 could be about 10 lbs or something.
NOTE Confidence: 0.927160284
00:14:06.160 --> 00:14:07.777 So you know this is what you
NOTE Confidence: 0.927160284
00:14:07.777 --> 00:14:08.999 might have expected from this.
NOTE Confidence: 0.927160284
00:14:09.000 --> 00:14:11.358 But just to show you we’re gaining the tools,
NOTE Confidence: 0.927160284
00:14:11.360 --> 00:14:11.824 the assays,
NOTE Confidence: 0.927160284
00:14:11.824 --> 00:14:13.680 the ability to use the real world data
within our own medical records to be able to ask important questions and be able to look at this kind of variation. The last thing I want to say quickly was we’re spending a lot of time thinking about how AI plays a role in this. We’ve got these amazing new capacity now with artificial intelligence. Would be crazy not to incorporate this into our research in ways that give us entirely new perspectives. I say despite the transformative advances in medicine and with these medicine, medicine itself remains largely anchored in an older era.
Our labels are antiquated.

I mean just saying this is a person with obesity without talking about subclasses, sub cohorts, really getting to a precision medicine, understanding what exactly does that person in front of you have. Our treatment decisions are largely based on average effects and our prognostic methods are quite limited.

AI is game changing for how we diagnose, predict and treat disease. And I think AI is going to relate to diagnosis, therapeutics and prognosis through these electronic digital signatures.
So in the lab, you guys are talking about deep immune, one of the work I'm doing with Akiko, deep immune phenotyping and she's developing signatures for different people based on lab assays. What we're going to be doing now is saying like how do we take digital information that's ubiquitous and to help us understand what condition does that person have in front of us? What's the best intervention that pairs with exactly who they are and what they need? And how do we optimize the outcomes and predict and prognosticate and
then modify what that prediction might be through not only the drug that we might use an example for using pharmacologic therapy, but how we surround that patient with other outcomes enhancing strategies for that particular pharmacologic agent and not really just think about all we have to do is write the script.

No, it’s a script surrounded by other information, particularly in a condition like obesity.

And then I’m saying these data signatures are really next generation phenotypes that
are going to depend on multimodal inputs.

So honestly, I'm agnostic actually to what the inputs are. As an outcomes researcher, I don't care. I want to know that I've got information coming from different knowledge domains. By contextual, I mean it may be different at this health system than somewhere else. Why are we succeeding more than they are?
What lessons can they glean if we're doing better than they are independent of everything else. Just saying by the context, the way we're set up, the clinics that we have, the kind of care that we deliver. So, So the other thing is we're developing strategic partnerships with groups that have aligned values, with groups that have aligned values, data and dissemination channels. Some of these I hope that we'll announce relatively soon that I think they'll blow you away by the kind of alignments that we're going.
to make in the teams that we’re going to work with who want to be able to have the same goals. We are and are going to help be a force multiplier effect for our access to data and channels for dissemination. And ultimately what we care about most, impact, impact is what we care about most. So our goal is to be the preeminent obesity outcomes research group within Y wait under Anya’s leadership to optimize the prevention and treatment of obesity and to improve population health. Thank you.
Questions for Harlan from the audience.

I’ve left you spellbound, crystal clear. So I’ll ask from lessons learned from other work that you’ve done.

How do you think we can engage patients with obesity in this work to help us better understand their needs, their experience? What do you think?

Yep. I mean, anya’s alluding to the fact that, but a lot of the work I’m doing now is trying to redesign the way that we do research in the sense of moving away from a hierarchical part where the researchers are on top and we work with subjects.
I don’t even use the word subjects ever anymore. I mean, I’m talking about partners, people who we guarantee that anything we do, we’re going to share those results back with you. We have town in some of the other work we do. We have town halls. We give people access to the investigators. We let them ask us questions, we give them, we post them on YouTube when we’re done. So the people who couldn’t make that meeting can find out about the study and what we’re learning. We we, we really push this agenda.
of saying you’re our partners,

we’re working together in common

cause no one has more motivation about trying to find answers than people

But so you tell me how is it that we lose people in trials otherwise is lose people in trials otherwise is

that people are lost to follow up.

They lose interest. They just follow up.

It’s because they get alienated.

They don’t feel as if we’re actually attentive to them.

my goal is that everybody’s in any studies, ours is delighted by the experience.
Will brag to their friends about how good it was and try to tell others they would do it again. And so that means that we constructed in a way that the any advances we make are ones that they can also feel good about. They can talk about it at the dinner table. They can recognize that we honor and respect their contribution that we guarantee that we’re going to tell them what we learn and we’re going to give them the credit that they deserve for taking the time to work with us to be able to do the work. So I think the people with
Obesity is a prime group to be able to pull in and learn from. By the way, I want to say with humility that it's not just that you do this because it's a good strategy to keep people in studies. It's a smart strategy if you want to be a good researcher because there's wisdom that resides in people who live with the conditions and we'd be well served to humbly learn from them when they've got things to tell us.

I wholeheartedly agree. Well, thank you for that wonderful talk, Harlan, and we are going to move forward with our final speaker for the day.