**COPE Presents:** “The Role of Diet in Chemotherapy Efficacy”

**Steven Mittelman, MD, PhD**

**January 13, 2021**

*Moderator: Lisa Diewald, MS, RD, LDN*

*Presenter: Steven D. Mittelman, MD, PhD*

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00:00:01.469 --> 00:00:06.270

Villanova Webinar 1: Good afternoon. Welcome to the first COPE webinar for health professionals in 2021.

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00:00:08.069 --> 00:00:13.830

Villanova Webinar 1: During these times when so many pandemic related changes have occurred in our personal and professional lives

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00:00:14.250 --> 00:00:26.640

Villanova Webinar 1: we're just so grateful that you've chosen to attend what promises to be an informal formative and insightful virtual continuing education opportunity. Today we will be exploring the role of diet in chemo therapeutic efficacy

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00:00:27.690 --> 00:00:34.230

Villanova Webinar 1: We have over 440 health professionals registered for this webinar. And we're so excited to get started.

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00:00:34.980 --> 00:00:44.070

Villanova Webinar 1: My name is Lisa Diewald. I'm the Program Manager for the MacDonald Center for Obesity Prevention and Education at Villanova University Fitzpatrick College of Nursing.

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00:00:44.490 --> 00:00:47.340

Villanova Webinar 1: I have the pleasure of being the moderator for today's webinar.

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00:00:48.210 --> 00:00:56.070

Villanova Webinar 1: While landmark advances in cancer treatment have led to improved outcomes, cancer remains the second leading cause of death in the United States.

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00:00:56.430 --> 00:01:05.850

Villanova Webinar 1: Strong associations exist between obesity and cancer, but there's still much to be learned about how diet influences the disease process after diagnosis.

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00:01:06.390 --> 00:01:15.390

Villanova Webinar 1: During this webinar. Dr. Steven Mittelman will present current evidence on how body weight and diet can impact cancer incidence and treatment outcome.

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00:01:16.380 --> 00:01:26.820

Villanova Webinar 1: Villanova University and Louise Fitzpatrick College of Nursing is home to the first College of Nursing in the country to have a center devoted exclusively to obesity prevention and education.

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00:01:27.540 --> 00:01:35.760

Villanova Webinar 1: COPE's goals are to enhance nursing education and topics related to nutrition obesity prevention and health promotion strategies.

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00:01:36.090 --> 00:01:44.310

Villanova Webinar 1: To provide continuing education programs such as this webinar on obesity and obesity related diseases for health professionals and educators

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00:01:44.610 --> 00:01:53.580

Villanova Webinar 1: And finally, to participate in research to expand and improve evidence based approaches for obesity prevention and education in the community.

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00:01:54.300 --> 00:02:04.950

Villanova Webinar 1: Before we begin the presentation, I would just like to remind you that PDFs of today's PowerPoint slides are located on the COPE website@villanova.edu slash cope

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00:02:05.730 --> 00:02:10.410

Villanova Webinar 1: After going to COPE's website, simply click on the webinar description page for this month's webinar.

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00:02:11.220 --> 00:02:16.140

Villanova Webinar 1: Please use the question and answer box on your screen to submit any questions for Dr Mittelman.

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00:02:16.590 --> 00:02:29.100

Villanova Webinar 1: All questions will be answered at the end of the program as time permits the expected length of the webinar is one hour the session, along with a transcript will be recorded and placed on the COPE website within the next week.

18

00:02:31.320 --> 00:02:45.120

Villanova Webinar 1: If you use your phone to call into the webinar today. And once the credit for attending the webinar, please take a moment afterwards to email us at cope@villanova.edu and provide your name, so that we can send you your CE certificate

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00:02:46.710 --> 00:02:58.410

Villanova Webinar 1: Villanova University M. Louise Fitzpatrick College of Nursing is accredited as a provider of nursing continuing professional development by the American Nurses Credentialing Center Commission on Accreditation.

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00:02:58.860 --> 00:03:10.800

Villanova Webinar 1: Villanova University College of Nursing Continuing Education/COPE is also a Continuing Professional education CPE Accredited Provider with the Commission on Dietetic Registration.

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00:03:12.480 --> 00:03:28.650

Villanova Webinar 1: Our webinar this month awards one contact our for nurses and one CPU for dietitians and DTRS. Performance Indicators are listed on the screen and the CDR level of this webinar is 2

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00:03:32.100 --> 00:03:35.100

Villanova Webinar 1: And now I have the pleasure of introducing today's speaker.

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00:03:36.120 --> 00:03:49.830

Villanova Webinar 1: Dr. Steven Mittelman MD PhD is Professor of Pediatrics, Division chief and Solomon and Maria M Kaplan Chair of Pediatric Endocrinology at UCLA Mattel Children's Hospital.

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00:03:50.250 --> 00:03:56.850

Villanova Webinar 1: He earned his PhD in physiology, and MD from Keck School of Medicine, University of Southern California.

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00:03:57.120 --> 00:04:03.690

Villanova Webinar 1: Dr Mittelman completed pediatric residency and endocrinology fellowships at the Children's Hospital Los Angeles

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00:04:03.930 --> 00:04:10.950

Villanova Webinar 1: where he became the founding director of the diabetes and obesity program and the Darnell Society for Pediatric Scientists.

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00:04:11.310 --> 00:04:22.080

Villanova Webinar 1: While pursuing research in the physiology of obesity, he became interested in the association between obesity and cancer, especially the link between obesity and leukemia outcome.

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00:04:22.560 --> 00:04:30.630

Villanova Webinar 1: Dr Mittelman is involved in several NIH NCI and private foundation sponsored obesity related research projects primarily focusing on

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00:04:30.960 --> 00:04:40.320

Villanova Webinar 1: understanding how childhood obesity effects physiology and leads to long term consequences and these investigations have led to over 60 publications

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00:04:41.190 --> 00:04:50.130

Villanova Webinar 1: We are thrilled he is able to join us today and present some of his research and evidence base and recommendations on the role of diet in chemotherapy therapy efficacy.

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00:04:51.960 --> 00:05:00.420

Villanova Webinar 1: While we're preparing for Dr. Mittelman's presentation to begin, I just wanted to mention that the planners and presenter of this webinar have no disclosures to report.

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00:05:00.840 --> 00:05:06.450

Villanova Webinar 1: The nurse planner and Planning Committee will evaluate the presentation for any evidence of commercial bias.

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00:05:06.870 --> 00:05:18.840

Villanova Webinar 1: Accredited status does not imply endorsement by Villanova University, COPE, or the American Nurses Credentialing Center of any commercial products or medical nutrition advice displayed in conjunction with an activity.

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00:05:19.260 --> 00:05:29.670

Villanova Webinar 1: And with that, I welcome Dr Mittelman to our COPE webinar program and I will virtually hand over the controls to him. Welcome, Dr. Mittelman.

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00:05:30.630 --> 00:05:39.030

Steven Mittelman (he/him), MD, PhD: Right. Well, thank you very much. I'm really thrilled to be here. I appreciate the invitation and I look forward to talking to you guys today.

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00:05:39.510 --> 00:05:50.070

Steven Mittelman (he/him), MD, PhD: Um, so I'm going to talk as Lisa said about the role of diet and chemotherapy efficacy and I'd like to do it by telling you a bit about my scientific journey,

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Steven Mittelman (he/him), MD, PhD: which is really, I think, a bedside to bench to bedside

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00:05:55.470 --> 00:06:08.070

Steven Mittelman (he/him), MD, PhD: journey. I'm going to go into a lot of the bench research I did, but I will try to keep it accessible and interesting to people who aren't so interested in basic science, but I do think it's important for us to understand

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00:06:08.970 --> 00:06:14.010

Steven Mittelman (he/him), MD, PhD: to some extent, at least the mechanisms behind what we're seeing, so we can best help our patients.

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Steven Mittelman (he/him), MD, PhD: So here are the objectives: to provide an overview on how body weight and diet can impact cancer incidence and treatment outcome and to understand the potential mechanisms whereby dietary intervention may improve chemotherapy efficacy.

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Steven Mittelman (he/him), MD, PhD: So my story began when I was a pediatric endocrine Fellow at Children's Hospital Los Angeles and and Anna Butturuni, who is an oncologist showed this slide at one of our noon conferences,

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Steven Mittelman (he/him), MD, PhD: where she reported data where you retrospectively looked back at kids who are diagnosed with high risk acute lymphoblastic leukemia, which is the most common cancer in children

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Steven Mittelman (he/him), MD, PhD: And she found that children who are obese at the time they were diagnosed had a worse survival, shown in yellow, compared to the ones who were not obese and the hazard ratio was actually 1.5 so a 50% increase risk of a worse survival.

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Steven Mittelman (he/him), MD, PhD: Now, it turns out that obesity as you probably all know is strongly related to cancer mortality.

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Steven Mittelman (he/him), MD, PhD: This was really the landmark study. I think that brought this to our attention by Eugenia Cali out of the American Cancer Society.

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Steven Mittelman (he/him), MD, PhD: They followed prospectively over 900,000 individuals and looked at their risk of death from a variety of different kinds of cancer, based on their BMI.

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Steven Mittelman (he/him), MD, PhD: And as you can see in both men and women, the risk of dying from cancers is significantly increased in the obese cohorts and it's not just one or two cancers but really quite the gamut of cancers.

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Steven Mittelman (he/him), MD, PhD: Dr. Kelly concluded based on her estimations that there's likely over 90,000 deaths per year from cancer that can be attributed to obesity and the American Institute for Cancer Research has come up with numbers, similar to that over 100,000.

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Steven Mittelman (he/him), MD, PhD: Now, as you might think about it, cancer mortality is a function of cancer incidence and cancer treatment failure rate or treatment outcome.

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Steven Mittelman (he/him), MD, PhD: And it's possible, and in fact, quite likely, that obesity could influence both, either or both of these factors to contribute to this increased cancer mortality.

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00:08:46.350 --> 00:09:01.590

Steven Mittelman (he/him), MD, PhD: So here is an infographic from one organization prevent obesity EU where they looked at the estimated relative risks of cancer incidence on the left cancer mortality on the right.

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00:09:02.220 --> 00:09:17.160

Steven Mittelman (he/him), MD, PhD: Based on obesity and as you can see in some of the cancers, particularly things like breast cancer and gall bladder cancer, you can see that the mortality risk seems to be higher than the incident risk. In other words,

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00:09:17.520 --> 00:09:27.600

Steven Mittelman (he/him), MD, PhD: the mortality is not just because of the increased incidence. Now you can't really compare these numbers exactly to each other because they're calculated in different ways,

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00:09:28.350 --> 00:09:39.660

Steven Mittelman (he/him), MD, PhD: but the evidence does show that obesity clearly increases cancer incidence this likely drives most of the effect of obesity to increase cancer mortality.

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00:09:40.230 --> 00:09:52.920

Steven Mittelman (he/him), MD, PhD: But there's also an effect of obesity to increase treatment failure, which is what I'm going to focus on for most of my talk. I just want to summarize here, and I'm sorry I lost the

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Steven Mittelman (he/him), MD, PhD: the tab down at the bottom. This is from Cancer Research UK this infographic just summarizes the three main hypotheses as to how obesity increases cancer incidence

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Steven Mittelman (he/him), MD, PhD: So number one is estrogen and as you're aware obese individuals have higher estrogen levels because fat tissue is actually a source of estrogen.

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00:10:19.770 --> 00:10:29.340

Steven Mittelman (he/him), MD, PhD: And so they tend to have higher estrogen levels over time, which can increase the incidence of particularly estrogen sensitive cancers and gynecological cancers.

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Steven Mittelman (he/him), MD, PhD: Number two. Obesity is associated often with high insulin levels and high levels of growth factors such as IGF insulin like growth factors and these are known to increase cancer.

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Steven Mittelman (he/him), MD, PhD: And number three is inflammation. So obesity is often talked about as a state of low grade inflammation

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Steven Mittelman (he/him), MD, PhD: perhaps stemming in part by the immune cells that infiltrate unhealthy adipose tissue and release cytokines and adipokines and inflammation has also long been known to increase the risk of cancer.

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00:11:10.320 --> 00:11:22.050

Steven Mittelman (he/him), MD, PhD: But I'm interested in how obesity might influence cancer treatment outcome. And as you know, obesity is not a simple phenotype, but associated with a number

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00:11:22.410 --> 00:11:41.820

Steven Mittelman (he/him), MD, PhD: of physical physiological psychological, social, economic, socio economic micro biome genetic differences any or all of which may contribute to a disproportionate failure rate of cancer treatment. So how can we

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00:11:42.930 --> 00:11:57.210

Steven Mittelman (he/him), MD, PhD: study this? And the answer is we need to go to preclinical models. So this is Nora Heistercamp.She had developed a mouse model of leukemia, where all of her mice have the VCR-able

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Steven Mittelman (he/him), MD, PhD: Gene oncogene, and they all develop leukemia and she worked at Children's Hospital la so I approached her and asked if we could make her mice obese.

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00:12:06.840 --> 00:12:18.570

Steven Mittelman (he/him), MD, PhD: And we did so with a high fat diet that's how mice get obese, not necessarily humans, but mice get obese, with a high fat diet and we observed to see if they would get leukemia faster.

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00:12:20.460 --> 00:12:30.360

Steven Mittelman (he/him), MD, PhD: And in fact, that they did tend to get leukemia faster. So the obese mice are shown in the solid line and the control mice in the dashed gray line and you can see that their survival

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00:12:31.350 --> 00:12:41.100

Steven Mittelman (he/him), MD, PhD: Tended to be lower in the P 190. These are the VCR- able we used another mouse model and spontaneous leukemia, the AKR and there was a more substantial effect.

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00:12:41.760 --> 00:12:50.670

Steven Mittelman (he/him), MD, PhD: These mice got leukemia, when they were older so maybe that's why. But in any case, this proved to me that there was a biological

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00:12:51.540 --> 00:12:58.830

Steven Mittelman (he/him), MD, PhD: signal that was related to the obesity, causing cancer or accelerating this leukemia progression.

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00:12:59.580 --> 00:13:16.230

Steven Mittelman (he/him), MD, PhD: These mice shared the same genetics, they shared the same behavior. They were very compliant with their diets, etc, etc. So this took out a lot of some of the social, economic and genetic factors that might contribute and and just narrowed it down to the biology.

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00:13:18.300 --> 00:13:29.670

Steven Mittelman (he/him), MD, PhD: But again, this is not looking at treatment failure and what I was really interested in was HOW this occurred. How do obese kids have a worse survival after treatment?

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00:13:30.960 --> 00:13:45.090

Steven Mittelman (he/him), MD, PhD: So to evaluate this, we had to change our model a little bit and instead of using genetically altered mice, we used wild type mice and we gave them cancer cells. We injected cancer cells on day zero

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00:13:45.750 --> 00:13:58.170

Steven Mittelman (he/him), MD, PhD: and then after a little period for those cancer cells to find the bone marrow and start growing, we treated them with chemotherapy shown in the gray bars and then the top you can see Vincristine and on the bottom, you can see two different forms of

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00:14:00.240 --> 00:14:18.510

Steven Mittelman (he/him), MD, PhD: L-asparaginase. And what we found was the obese mice, shown again in the solid line, had a worst survival than the non obese mice, shown in the dark dashed lines with all three of these forms of chemotherapy. These chemotherapies were given by gram of body weight. So

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00:14:20.310 --> 00:14:31.830

Steven Mittelman (he/him), MD, PhD: relatively at a higher dose than we give obese patients because a lot of these chemos and patients are either capped or given by body surface area or ideal body weight, as you know.

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Steven Mittelman (he/him), MD, PhD: So despite giving higher doses relatively these mice had a worse outcome somewhat similar to what we see in the kids.

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00:14:43.050 --> 00:14:52.470

Steven Mittelman (he/him), MD, PhD: Now, when we looked at some of these mice that developed leukemia, despite treatment we found leukemia cells, shown here in yellow, hiding in the fat tissue.

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00:14:52.920 --> 00:15:08.940

Steven Mittelman (he/him), MD, PhD: Okay, I say hiding. I think they're hiding, but I can't really prove that they're hiding, but they're there in the fat tissue. And so we wondered if maybe there was some interaction between fat cells that might be the mediator of this relationship between obesity and cancer.

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Steven Mittelman (he/him), MD, PhD: This actually shows a bone marrow

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Steven Mittelman (he/him), MD, PhD: from a mouse, and it's just a pretty little picture you can see adipocytes these big red adipocytes in the bone marrow and the leukemia cells, these little green cells just hanging around these adipocytes.

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00:15:29.610 --> 00:15:39.090

Steven Mittelman (he/him), MD, PhD: So one of the first things we wondered is is the leukemia cell in the fat because it just goes everywhere, or is it particularly going to fat tissue?

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00:15:39.750 --> 00:15:51.030

Steven Mittelman (he/him), MD, PhD: And so to study this Rocky Pramaninik and Susan Shang in my lab set of this assay, where we took fat tissue either fat cells or fat tissue from a mouse and put it in the bottom of this

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00:15:51.510 --> 00:16:01.710

Steven Mittelman (he/him), MD, PhD: What's called a Boyden chamber and we put leukemia cells in the top and these are separated by a screen door of a sort that's big enough that the leukemia cells can squeeze through it.

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00:16:03.030 --> 00:16:10.860

Steven Mittelman (he/him), MD, PhD: And what we found is that when there is fat in the bottom, the leukemia cells migrate quite rapidly. This is within 90 minutes

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00:16:11.340 --> 00:16:15.810

Steven Mittelman (he/him), MD, PhD: You can see, you know, 15 to 20% of the leukemia cells migrated towards the fat.

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00:16:16.560 --> 00:16:27.450

Steven Mittelman (he/him), MD, PhD: The left bar is no tissue. So there was really no spontaneous migration and the right bar is muscle so they weren't going to muscle. They were specifically heading towards the fat tissue.

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00:16:27.900 --> 00:16:37.050

Steven Mittelman (he/him), MD, PhD: And we actually identified the chemo kind called stromal-derived factor-1 that the fats, it creates that actually attracts the leukemia cells into the fat.

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00:16:40.020 --> 00:16:48.330

Steven Mittelman (he/him), MD, PhD: But who cares if they get into fat. What does that. What does that matter. Well, we wondered if the fat cells might protect leukemia cells from chemotherapy.

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00:16:48.960 --> 00:16:56.550

Steven Mittelman (he/him), MD, PhD: So to study that we changed our model a little bit we used what's called a transwell system where we could put leukemia cells in the top

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00:16:56.940 --> 00:17:05.550

Steven Mittelman (he/him), MD, PhD: This time the screen door is too tight for the leukemia cells to go through. It's a 0.4 micron and then we have fat cells in the bottom and this shared media.

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00:17:06.240 --> 00:17:13.620

Steven Mittelman (he/him), MD, PhD: And when we add chemotherapy. This is Jim Behan in my lab that did these studies, you can see that if there are fat cells in the bottom,

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00:17:14.070 --> 00:17:26.280

Steven Mittelman (he/him), MD, PhD: The leukemia cells survive treatment with all five of these chemotherapies much better than if there are control tissue fibroblasts in the bottom or if there's no cells in the bottom shown in grey.

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00:17:27.300 --> 00:17:41.070

Steven Mittelman (he/him), MD, PhD: Now these are five chemotherapies that we're giving to kids with leukemia and they have five different mechanisms of action. So there seems to be some overarching effect of fat cells to protect leukemia cells from chemotherapy.

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00:17:43.500 --> 00:18:01.290

Steven Mittelman (he/him), MD, PhD: So based on these findings we wondered, how could fat cells protect the leukemia cells from chemotherapy? And we came up with a list of possibilities. So one- perhaps the fat cells are releasing some factors that signal the leukemia cells to survive.

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00:18:02.460 --> 00:18:14.040

Steven Mittelman (he/him), MD, PhD: 2- perhaps they're providing fuel to leukemia cells and 3- What if they're stopping up the chemotherapy, they're absorbing it like a sponge and therefore the chemotherapy is unable to kill the leukemia cells?

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00:18:15.210 --> 00:18:24.810

Steven Mittelman (he/him), MD, PhD: And I'm going to go pretty quick through all of this because it's a lot of work and a lot of detail, but I'm going to give you a kind of a high level overview of our studies that found all three of these effects.

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00:18:26.040 --> 00:18:34.680

Steven Mittelman (he/him), MD, PhD: So first, secreting factors. So as I showed, we used to a transwell system where the leukemia cells were not touching the fat cells, but they were

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00:18:35.700 --> 00:18:47.100

Steven Mittelman (he/him), MD, PhD: They were sharing the same media and when we did this, we looked at some survival signals in the leukemia cells and found that if there was fat cells in the bottom shown in the black bar,

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00:18:47.820 --> 00:19:01.200

Steven Mittelman (he/him), MD, PhD: These, these survival signals were higher than if there weren't and the western blot shows the same thing. Higher levels of anti apoptonic signals that that tell the leukemia cells to survive.

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00:19:03.630 --> 00:19:04.020

Steven Mittelman (he/him), MD, PhD: And

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00:19:05.310 --> 00:19:13.200

Steven Mittelman (he/him), MD, PhD: I'm showing you. Again, this. The Trans Well data with the Daunorubicin and so we reasoned that if the

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00:19:14.610 --> 00:19:17.250

Steven Mittelman (he/him), MD, PhD: If the fat cells were protecting the leukemia cells.

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00:19:17.790 --> 00:19:26.070

Steven Mittelman (he/him), MD, PhD: From Daunorubicin and they were secreting something that we should just be able to take this media from the fat cells and see if it protects. And so we did that. We took fat cells.

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00:19:26.610 --> 00:19:33.990

Steven Mittelman (he/him), MD, PhD: We let them secrete whatever they were going to secrete . We took that media and we call that adipocyte- conditioned media.

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00:19:34.620 --> 00:19:49.140

Steven Mittelman (he/him), MD, PhD: And then we put leukemia cells in that media and treated them with Daunorubicin and we were somewhat crushed and surprised to find that that adipocyte-onditioned media did nothing to protect the leukemia cells. These are two different adipocytes cell lines we use

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00:19:50.430 --> 00:19:55.140

Steven Mittelman (he/him), MD, PhD: Despite this huge effect in the trans well there didn't seem to be

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00:19:56.250 --> 00:19:58.110

Steven Mittelman (he/him), MD, PhD: Anything secreted that we could detect

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00:19:59.370 --> 00:20:14.160

Steven Mittelman (he/him), MD, PhD: So we scratched our heads a little bit and tried to figure out how these two bits of data could possibly both exist. And then we wondered, well, maybe the fat cells are not releasing some protective factor unless there's leukemia cells there.

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00:20:15.390 --> 00:20:23.040

Steven Mittelman (he/him), MD, PhD: So the test for that we took leukemia cells and fat cells together. Let them secrete whatever they were going to secrete

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00:20:23.760 --> 00:20:36.480

Steven Mittelman (he/him), MD, PhD: We call this adipocyte leukemia cells condition media and then we put leukemia cells in that and treated them with Daunorubicin and lo and behold, that protected the leukemia cells from Daunorubicin

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00:20:37.950 --> 00:20:44.580

Steven Mittelman (he/him), MD, PhD: So the leukemia cells and fat cells are communicating. They're talking in this two way communication, where

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00:20:45.060 --> 00:20:56.580

Steven Mittelman (he/him), MD, PhD: the leukemia cells, I picture it they're asking the fat cells to protect them and the fat cells are obliging by releasing some protective factors. We don't know what these signals are yet we're still working on that.

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00:20:59.340 --> 00:21:11.370

Steven Mittelman (he/him), MD, PhD: Okay, what about providing metabolic fuels to leukemia cells. So as you know, fat, fat tissue. Its main job is to store fuel and provide it in the times that it's needed.

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00:21:12.210 --> 00:21:20.760

Steven Mittelman (he/him), MD, PhD: So perhaps they're providing fuel to leukemia cells. Cancers need a lot of fuel because they're rapidly dividing and making a lot of protein.

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00:21:23.280 --> 00:21:25.800

Steven Mittelman (he/him), MD, PhD: Well Ehsanipour and Vassilios Avramis

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00:21:26.880 --> 00:21:35.310

Steven Mittelman (he/him), MD, PhD: looked and found that in fact fat cells are releasing two very important amino acids for leukemia cells, asparagine and glutamine.

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00:21:36.060 --> 00:21:43.650

Steven Mittelman (he/him), MD, PhD: Asparagine is particularly important to actually both of these are particularly important because one of the treatments for leukemia is L-asparaginase,

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00:21:44.070 --> 00:21:53.910

Steven Mittelman (he/him), MD, PhD: which acts by reducing or breaking down the asparagine, and to a lesser extent, the glutamine and the blood and the leukemia cells need these amino acids.

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00:21:54.810 --> 00:22:02.760

Steven Mittelman (he/him), MD, PhD: But if the fat is producing it, then right there. It might be providing on those amino acids and helping the leukemia cells to resist that chemotherapy.

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00:22:05.970 --> 00:22:16.200

Steven Mittelman (he/him), MD, PhD: And what about fat. Well, Jonathan Tucci was an MD PhD student in my lab and we wanted to see if the fat cells might be giving free fatty acids to the leukemia.

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00:22:16.800 --> 00:22:28.740

Steven Mittelman (he/him), MD, PhD: So he took our cultured fat cells and he treated them with a fluorescently labeled free fatty acid called bodipy. And then he put leukemia cells in

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00:22:29.430 --> 00:22:40.410

Steven Mittelman (he/him), MD, PhD: And found that those leukemia cells are pretty rapidly became fluorescent. So this is a flow cytometry, and you don't need to understand it but just to show that on this.

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00:22:41.010 --> 00:22:48.300

Steven Mittelman (he/him), MD, PhD: The fluorescent signal went up within you know two to four hours the leukemia cells became fluorescent and took up these

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00:22:49.530 --> 00:23:02.370

Steven Mittelman (he/him), MD, PhD: Fluorescently labeled free fatty acids from the fat cells. And this is what that looks like. You can see that the fluorescent label went into these droplets and maybe into some membranes of the leukemia cells.

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00:23:03.630 --> 00:23:09.420

Steven Mittelman (he/him), MD, PhD: And in fact, even if you just take leukemia cells and and don't put them with fat, they have lipid droplets

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00:23:10.620 --> 00:23:20.220

Steven Mittelman (he/him), MD, PhD: And we were surprised we wondered if they use these lipid droplets, or what. Therefore, we took leukemia cells and they have lipid droplets on the left, and we put them in a low fuel media

128

00:23:20.490 --> 00:23:34.530

Steven Mittelman (he/him), MD, PhD: for a while, and those lipid droplets disappeared and then we put them back in normal media and those liquid droplets came back. So it seems like the leukemia cells like to have fat around. They kind of need it and they can use it and store it.

129

00:23:38.190 --> 00:23:49.770

Steven Mittelman (he/him), MD, PhD: And to make matters even more interesting. We found that the fat cells release more free fatty acids, when there's leukemia cells around. So when the fat cells are

130

00:23:50.370 --> 00:23:56.760

Steven Mittelman (he/him), MD, PhD: In what we call the leukemia condition media shown in the upper left the dark bar. They released more of these fat.

131

00:23:57.540 --> 00:24:02.220

Steven Mittelman (he/him), MD, PhD: And the right show just shows that the leukemia cells can reduce the amount of fat in the media.

132

00:24:03.030 --> 00:24:19.800

Steven Mittelman (he/him), MD, PhD: And when we use this drug called Tofa on the bottom which inhibits the leukemia cells from making its own free fatty acids that was very toxic to the leukemia cells. But if there were fat cells in that culture, it was less toxic shown in the top top

133

00:24:20.820 --> 00:24:33.750

Steven Mittelman (he/him), MD, PhD: line. So it seems it appears that the fat cells can produce free fatty acids, give them to the leukemia cells and that allows the leukemia cells to not have to make their own free fatty acids.

134

00:24:36.540 --> 00:24:45.390

Steven Mittelman (he/him), MD, PhD: Now this is very complicated. So I'm not going to go too much into it. But there's these cool machines nowadays that can actually measure the cellular metabolism.

135

00:24:45.840 --> 00:24:51.390

Steven Mittelman (he/him), MD, PhD: And these are the cell metabolism of leukemia cells after they've been cultured with fat cells.

136

00:24:51.840 --> 00:25:07.710

Steven Mittelman (he/him), MD, PhD: And just on the left, you can see that on day three, after three days of culture, the metabolism of the leukemia cells drops shown in the dark circles. If they've been with fat cells. So the fat cells are providing energy and they can slow down their metabolic rate.

137

00:25:08.790 --> 00:25:16.980

Steven Mittelman (he/him), MD, PhD: On the bottom graphs just showed that they can use fat if they've been with the fat cells, but they don't use as much fat when they're just by themselves.

138

00:25:19.410 --> 00:25:31.920

Steven Mittelman (he/him), MD, PhD: And this just I was proud of this western blot because it took forever to get it to work right. But it shows that when leukemia cells are cultured with adipocytes they upregulate

139

00:25:32.460 --> 00:25:41.190

Steven Mittelman (he/him), MD, PhD: something called CPT 1A, which is carnitine palmityl transferance transfers. It's the rate limiting step for fat metabolism or fat oxidation

140

00:25:41.910 --> 00:25:50.340

Steven Mittelman (he/him), MD, PhD: And they increase phosphorylation of pyruvate dehydrogenase, which is the signal that tells the cell to use fat instead of glucose.

141

00:25:50.970 --> 00:26:07.110

Steven Mittelman (he/him), MD, PhD: So I'm putting this all together that when there's a leukemia cell around fat, it starts to depend on the fat coming from the fat cell and it can relieve some of the metabolic requirements of the leukemia cell.

142

00:26:09.660 --> 00:26:21.300

Steven Mittelman (he/him), MD, PhD: Okay, now the third possibility we came up with was, what if the fat cells are absorbing the chemotherapies and so to test this Susan Sheng in my lab.

143

00:26:22.080 --> 00:26:30.150

Steven Mittelman (he/him), MD, PhD: Again, we took our fat so model and we added Daunorubicin and Daunorubicin fluorescences so it's a really nice

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00:26:30.870 --> 00:26:39.180

Steven Mittelman (he/him), MD, PhD: way we can look at it. We added Daunorubicin to the media and let that sit there for a while and we hypothesized that maybe the fat cells would absorb that Daunorubicin

145

00:26:40.110 --> 00:27:00.630

Steven Mittelman (he/him), MD, PhD: In fact, when we then took that media and treated leukemia cells with it, the media had been detoxified by the adipocytes. So you can see, even with extremely high concentrations of Daunorubicin if it had sat for 48 hours over fat cells, it was detoxifying, to a large degree.

146

00:27:01.740 --> 00:27:12.000

Steven Mittelman (he/him), MD, PhD: We then split open these fat cells to see if they still had Daunorubicin in it. And in fact, they did have some Daunorubicin or some toxicity. Not as much as we would expect.

147

00:27:12.720 --> 00:27:18.840

Steven Mittelman (he/him), MD, PhD: So that actually made us wonder if the fat cells were not only absorbing the Daunorubicin but maybe breaking it down.

148

00:27:20.880 --> 00:27:33.090

Steven Mittelman (he/him), MD, PhD: This is what these fat cells look like these are cultured fat cells, so they're different than fat cells you might see in an actual body and they have a lot of small lipid droplets instead of one large lipid droplet like an intact fat cell.

149

00:27:34.230 --> 00:27:44.730

Steven Mittelman (he/him), MD, PhD: But the Daunorubicin which fluoresces red just goes into these fat cells and it doesn't go into the liquid; surprisingly goes into the cytoplasm, so very interesting.

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00:27:46.230 --> 00:27:58.590

Steven Mittelman (he/him), MD, PhD: Now, to see if they were breaking it down, we worked with Stan Louie over at USC, who has a mass spectrometry method to measure Daunorubicin and its breakdown product Daunorubicin-ol

151

00:27:59.430 --> 00:28:08.430

Steven Mittelman (he/him), MD, PhD: And if you just look at the bottom left, the media that had been over either no cells shown in white.

152

00:28:08.910 --> 00:28:22.770

Steven Mittelman (he/him), MD, PhD: If you keep media just for 48 hours in the culture in the incubator, nothing happens to the Daunorubicin shown in white, but if you put it over fiberglass or especially if you put it over fat cells that Daunorubicin rapidly goes away.

153

00:28:24.330 --> 00:28:33.480

Steven Mittelman (he/him), MD, PhD: Now, if you look at Daunorubicin-ol on the right you see the opposite pattern. If there's fat cells in the media a lot of that Daunorubicin is turned into Daunorubicin-ol

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00:28:33.900 --> 00:28:42.270

Steven Mittelman (he/him), MD, PhD: That Daunorubicin-ol is a fairly inactive compared to Daunorubicin so the fat cells are inactivating this chemotherapy.

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00:28:43.380 --> 00:28:56.550

Steven Mittelman (he/him), MD, PhD: And just, if you look at the upper left, you can see that if you put leukemia cells in with those fat cells,they accumulate much less Daunorubucin shown in the stripe than if they're cultured by themselves.

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00:28:59.100 --> 00:29:07.590

Steven Mittelman (he/him), MD, PhD: And this just shows,this is based on just online proteomics data, we found that fat cells express a lot of

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00:29:08.430 --> 00:29:21.330

Steven Mittelman (he/him), MD, PhD: enzymes called AKR enzymes altoketoreductase enzymes that are the ones that break down Daunorubicin so you can see they have really high expression of these- higher than pretty much any other tissue, except maybe liver

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00:29:22.590 --> 00:29:26.490

Steven Mittelman (he/him), MD, PhD: So they're professional "chemotherapy breaker-downers."

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00:29:28.170 --> 00:29:41.370

Steven Mittelman (he/him), MD, PhD: And this just shows a bone marrow biopsy from a kid with leukemia and the brown just shows these enzymes, we stain for these enzymes. And you can see that the fat cells, there's a lot of brown here with all of these

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00:29:42.480 --> 00:29:47.190

Steven Mittelman (he/him), MD, PhD: Daunorubicin break down enzymes compared to the lower right, which is the negative control.

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00:29:50.190 --> 00:29:54.360

Steven Mittelman (he/him), MD, PhD: Okay, so I know that was fast. That was probably 15 years worth of work.

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00:29:55.170 --> 00:30:01.740

Steven Mittelman (he/him), MD, PhD: But I wanted to get to the clinical and translational part, so I wanted to go quick. But here is a kind of an overview of what I've shown you.

163

00:30:02.460 --> 00:30:16.170

Steven Mittelman (he/him), MD, PhD: So we have fat tissue. It's in our fats. We have fat cells in our fat tissue. It's in our bone marrow and these cells release chemokines like SDF1-alpha that attracts leukemia cells into that micro environment.

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00:30:17.070 --> 00:30:23.400

Steven Mittelman (he/him), MD, PhD: We give chemotherapy, but of course we give the chemotherapy into the bloodstream and it has to diffuse into these micro environments.

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00:30:24.210 --> 00:30:33.900

Steven Mittelman (he/him), MD, PhD: We found that fat cells absorb some chemotherapies. I didn't show it, but they absorb vincristine and Daunorubicin and they actually break down Daunorubicin

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00:30:34.620 --> 00:30:50.820

Steven Mittelman (he/him), MD, PhD: I also didn't show, but the fat cells release hydrogen peroxide, which I think also breaks down Daunorubicin. So all of these things together, likely contribute to a gradient, where there's less active chemotherapy in the fat micro environment.

167

00:30:52.260 --> 00:31:07.710

Steven Mittelman (he/him), MD, PhD: Further, we showed that fat cells released some survival signals which allow the leukemia cells to survive and menacingly the leukemia cells interact with the fat cells to tell them to release more of these or maybe other survival signals.

168

00:31:09.270 --> 00:31:20.700

Steven Mittelman (he/him), MD, PhD: And then finally, the fat cells are providing fuels like amino acids and free fatty acids to the leukemia cells, which probably also contributes to their proliferation and survival.

169

00:31:22.470 --> 00:31:31.830

Steven Mittelman (he/him), MD, PhD: Now, I've been talking about leukemia, because that's what I'm interested in. I'm a pediatrician, but a lot of these things are likely happening in other cancers as well.

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00:31:32.340 --> 00:31:50.130

Steven Mittelman (he/him), MD, PhD: I showed you earlier that obesity is associated with higher mortality from a wide variety of cancers. Many Cancers find their way into fat tissue because they're either close to it like colon cancer and breast cancer or pancreatic cancer has been shown to

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00:31:51.240 --> 00:32:06.840

Steven Mittelman (he/him), MD, PhD: accumulate fat cells in the cancer itself in some mouse models. So these interactions that we're seeing are likely not just related to leukemia, but could be related to a lot of other cancers as well.

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00:32:10.050 --> 00:32:16.260

Steven Mittelman (he/him), MD, PhD: Okay, now I've been showing you the biological determinants, but especially in this day and age, I think it's very important

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00:32:16.650 --> 00:32:26.040

Steven Mittelman (he/him), MD, PhD: That we also keep in mind, social determinants. So this is not my field of study, which is why I don't focus on it. But I do think it's really important to mention

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00:32:26.430 --> 00:32:35.160

Steven Mittelman (he/him), MD, PhD: That there are a lot of social determinants that can also contribute to worse mortality, in obese patients. So, for example,

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00:32:35.790 --> 00:32:41.070

Steven Mittelman (he/him), MD, PhD: there are studies that show that obese patients have lower rates of cancer screening, some of that is

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00:32:41.550 --> 00:32:51.480

Steven Mittelman (he/him), MD, PhD: because they are less comfortable going in for cancer screening and some of that, unfortunately, it's because the health care team is less comfortable doing the screening tests on obese patients.

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00:32:52.710 --> 00:33:02.550

Steven Mittelman (he/him), MD, PhD: Clearly obese individuals may have different dietary patterns that might contribute to increase intake of carcinogens, for example, or

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00:33:04.080 --> 00:33:07.470

Steven Mittelman (he/him), MD, PhD: foods that maybe promote carcinogenesis

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00:33:09.060 --> 00:33:23.580

Steven Mittelman (he/him), MD, PhD: Poverty itself is associated with cancer incidence and increased mortality poverty has been called a carcinogen and I really believe it. And of course, as you know, obesity is more prevalent and often has more

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00:33:25.110 --> 00:33:35.250

Steven Mittelman (he/him), MD, PhD: More morbidity associated with it and underrepresented minorities its associated with lower socioeconomic status, a disparate access to healthcare.

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00:33:36.300 --> 00:33:47.040

Steven Mittelman (he/him), MD, PhD: burdens of other diseases, perhaps because have less access to healthcare and less inclusion in clinical trials and this is you know multifactorial

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00:33:48.330 --> 00:33:58.710

Steven Mittelman (he/him), MD, PhD: People of underrepresented minorities are likely less likely to be treated at academic centers where they would have better access to clinical trials.

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00:33:59.580 --> 00:34:12.180

Steven Mittelman (he/him), MD, PhD: But also, you know, the medical community has done some bad things, and quite a disservice, and there might be a loss of trust, still in underrepresented minorities to enroll in clinical trials.

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00:34:15.480 --> 00:34:25.200

Steven Mittelman (he/him), MD, PhD: Okay, so an obvious question based on all of this data I showed you is should we intervene, should we be doing something to

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00:34:25.710 --> 00:34:30.000

Steven Mittelman (he/him), MD, PhD: address the obesity and maybe improve outcome from leukemia and I'm going to give you some

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00:34:30.600 --> 00:34:38.190

Steven Mittelman (he/him), MD, PhD: evidence of why we should. So first of all, Aton Orgel is an oncologist at Children's Hospital LA who I collaborate with quite closely.

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00:34:38.700 --> 00:34:48.810

Steven Mittelman (he/him), MD, PhD: He again retrospectively looked at kids who were obese versus not obese at diagnosis, but then he looked at those who became non obese during their treatment.

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00:34:49.320 --> 00:34:55.110

Steven Mittelman (he/him), MD, PhD: So if they were not obese for over 50% of the time after their maintenance therapy after the startup maintenance.

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00:34:55.800 --> 00:35:10.950

Steven Mittelman (he/him), MD, PhD: He looked at them differently than those who were obese less than 50%. So if they started obese and become non obese, they were on this red line and you can see they had a better outcome. So maybe the effect of obesity could be reversed.

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00:35:12.420 --> 00:35:31.440

Steven Mittelman (he/him), MD, PhD: We tested this in our mouse model. So again, we took control and obese mice. We gave them leukemia at day zero here, but then after the leukemia had time to develop we switched some of the obese mice to the control low fat diet and then we gave them chemotherapy.

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00:35:32.730 --> 00:35:42.450

Steven Mittelman (he/him), MD, PhD: And if you just look at the center graph here labeled "C", you can see that the again the obese mice that stayed on the obese diet had a really bad outcome. Almost all of them died.

192

00:35:42.990 --> 00:35:53.010

Steven Mittelman (he/him), MD, PhD: The obese mice that were dieted almost all of them survived. And in fact, they had better survival than the control mice, who were still on that low fat diet, since they were born the same low fat diet.

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00:35:53.910 --> 00:36:03.390

Steven Mittelman (he/him), MD, PhD: So something about switching the diet right before chemotherapy or right when chemotherapy was starting seem to protect those diet and mice from Vincristine

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00:36:04.860 --> 00:36:19.770

Steven Mittelman (he/him), MD, PhD: Now, in full disclosure, we did the same experiment with two other chemotherapies- dexamethasone and L-asparaginase and we did not see this effect. So this may not be a universal effect. We're still teasing out which chemotherapies are affected by this diet.

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00:36:22.290 --> 00:36:37.080

Steven Mittelman (he/him), MD, PhD: Okay, another reason we should consider intervening is that kids with ALL, you know, especially in LA, where we have a very large Latinx population, a lot of them come in overweight or obese almost 50%.

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00:36:38.070 --> 00:36:50.340

Steven Mittelman (he/him), MD, PhD: And during that first month of chemotherapy which is called induction and you can see we looked at body fat and the body fat percentage just in that one month goes up by about a quarter.

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00:36:53.220 --> 00:36:56.610

Steven Mittelman (he/him), MD, PhD: And not only does their whole body fat go up, but their bone marrow

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00:36:57.120 --> 00:37:06.330

Steven Mittelman (he/him), MD, PhD: fat cells increase. So this is a bone marrow biopsy from a kid at day one diagnosis. You can see it's full of leukemia. Well, maybe you can't see if you have to trust me, that's all leukemia.

199

00:37:06.870 --> 00:37:17.550

Steven Mittelman (he/him), MD, PhD: But after that first month of chemotherapy when they test to see if there's any leukemia cells left in the bone marrow, you can see that most of the bone marrow is taken over by these big white fat cells.

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00:37:18.330 --> 00:37:23.040

Steven Mittelman (he/him), MD, PhD: A lot of this is probably from the steroids that we give these kids as part of their treatment.

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00:37:25.140 --> 00:37:26.640

Steven Mittelman (he/him), MD, PhD: But there might be other effects as well.

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00:37:28.620 --> 00:37:29.250

Steven Mittelman (he/him), MD, PhD: And

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00:37:30.360 --> 00:37:41.670

Steven Mittelman (he/him), MD, PhD: You know, we look to see if there might be an effect on obesity, on the number of individuals who have surviving leukemia cells in their bone marrow

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00:37:42.120 --> 00:37:52.590

Steven Mittelman (he/him), MD, PhD: after that first month of treatment. In fact, we found that there's over a two, two and a half fold increased risk that even after that first month of treatment if you're obese, you have

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00:37:53.340 --> 00:38:02.820

Steven Mittelman (he/him), MD, PhD: detectable leukemia in your bone marrow. This is probably the number one prognostic factor or one of the most important prognostic factors for survival for leukemia. So this is a huge

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00:38:03.840 --> 00:38:17.760

Steven Mittelman (he/him), MD, PhD: issue, but it also tells us that if we are going to intervene with a diet, we need to do it before day 29 and based on my mouse data, we probably need to do it right when chemotherapy starts, if not before.

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00:38:20.100 --> 00:38:31.470

Steven Mittelman (he/him), MD, PhD: So based on all of this Dr. Orgeland I developed the IDEAL trial. IDEAL stands for Improving Diet and Exercise in Acute Lymphoblastic Leukemia. I'm very proud of that acronym.

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00:38:32.070 --> 00:38:38.310

Steven Mittelman (he/him), MD, PhD: And this was an individualized obesity intervention with the goal of mitigating that fat gain

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00:38:39.210 --> 00:38:50.220

Steven Mittelman (he/him), MD, PhD: I showed you, and also to prevent some muscle loss if possible during induction. And then, of course, to reduce the minimal residual disease, the number of kids who have surviving leukemia cells after that first month.

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00:38:52.650 --> 00:39:06.870

Steven Mittelman (he/him), MD, PhD: And so, you know, the intervention only lasted during the first month of treatment. So it was very limited. It was a modest diet. It was a 10% calorie reduction

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00:39:08.010 --> 00:39:17.370

Steven Mittelman (he/him), MD, PhD: with maintenance of protein requirements. To try to help maintain that lean body mass, we lowered the glycemic load

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00:39:18.270 --> 00:39:29.670

Steven Mittelman (he/him), MD, PhD: if possible, and we lowered the fat intake. But it was a very modest diet and it was very modest because these kids are being treated with leukemia. It's a horrible time for them both

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00:39:30.120 --> 00:39:36.720

Steven Mittelman (he/him), MD, PhD: physically and emotionally and psychologically and this has never been done during the initial phases of treatment,

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00:39:37.680 --> 00:39:50.160

Steven Mittelman (he/him), MD, PhD: where you know these kids are getting several chemotherapies during this this period. So that's why we did such a modest diet. We also did an activity intervention with a physical therapist

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00:39:51.210 --> 00:39:59.490

Steven Mittelman (he/him), MD, PhD: where the dietitian and physical therapists met with the patient, physically, at least once a week, and while they were hospitalized at the beginning of induction.

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00:40:01.560 --> 00:40:06.090

Steven Mittelman (he/him), MD, PhD: So did we do anything to body composition? Well, not a whole lot,

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00:40:06.660 --> 00:40:13.470

Steven Mittelman (he/him), MD, PhD: so we compared this to this was not a randomized trial. This was a pilot trial we compared to recent historical controls.

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00:40:13.860 --> 00:40:27.780

Steven Mittelman (he/him), MD, PhD: And as you can see the kids who started out lean, they all gained a body fat and it didn't seem to matter which group they were in, but the kids who started out overweight or obese, it does look like the ones that were in our trial actually had less accumulation of fat mass

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00:40:28.800 --> 00:40:34.500

Steven Mittelman (he/him), MD, PhD: Lean mass dropped in all subjects, no matter what were they were so we really didn't do anything on that end.

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00:40:36.210 --> 00:40:45.060

Steven Mittelman (he/him), MD, PhD: What about physiology? Well, one thing we looked at is called the Adipokine to leptin ratio, which is kind of a surrogate for insulin sensitivity

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00:40:45.510 --> 00:40:57.810

Steven Mittelman (he/him), MD, PhD: And we saw that by the end of induction shown EOI so day 29 the kids in our ideal intervention had a higher Adipoline to leptin ratio

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00:40:58.710 --> 00:41:06.060

Steven Mittelman (he/him), MD, PhD: than those who are in the historical control whether they started out lean or overweight or obese and we were really pleased to note that

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00:41:06.690 --> 00:41:18.270

Steven Mittelman (he/him), MD, PhD: fewer kids required exogenous insulin in the IDEAL trial than in the historical control. We did random insulin levels. We didn't have access to fasting, there were significantly lower

224

00:41:20.100 --> 00:41:38.850

Steven Mittelman (he/him), MD, PhD: but most importantly, we reduced minimal residual disease. So the odds ratio was 0.3. So we reduce the risk of having detectable minimal residual disease by about 70%. This was done in a multivariate analysis

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00:41:39.960 --> 00:41:53.760

Steven Mittelman (he/him), MD, PhD: correcting for all other known risk factors are commonly used risk factors. So based on this, we actually proposed and just got funding from the NCI to do a multicenter randomized

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00:41:55.110 --> 00:42:04.320

Steven Mittelman (he/him), MD, PhD: controlled trial which is being done through a consortium and we got a really good score and the funding should be starting this fall.

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00:42:07.350 --> 00:42:16.320

Steven Mittelman (he/him), MD, PhD: Okay, now I want to talk. So this was my stuff. I want to talk about the state of the literature as far as diets on

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00:42:16.890 --> 00:42:26.010

Steven Mittelman (he/him), MD, PhD: cancer treatment outcome, and unfortunately, there's not a whole lot of literature. I did just write a review article for annual reviews of nutrition.

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00:42:26.400 --> 00:42:34.830

Steven Mittelman (he/him), MD, PhD: and I think I showed the reference at the end. If you want to get into the nitty gritty of it, but I'm just summarizing here what what I found. So

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00:42:35.280 --> 00:42:56.430

Steven Mittelman (he/him), MD, PhD: there have been some fasting trials and most fasting trials in the preclinical models show the benefit of fasting to slow cancer progression and it does seem to improve treatment outcomes of these cancers listed here. Again, these are preclinical trials. But there seems to be a signal.

231

00:42:57.840 --> 00:43:01.140

Steven Mittelman (he/him), MD, PhD: Interestingly, if you use their you can use

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00:43:02.460 --> 00:43:06.930

Steven Mittelman (he/him), MD, PhD: immunocompromised models where you actually can put human cancers into mice.

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00:43:07.440 --> 00:43:15.570

Steven Mittelman (he/him), MD, PhD: So you're studying a human cancer, but you're studying in a mice that doesn't have an immune system. So, you know, you get some benefit from that. But maybe some downside.

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00:43:16.260 --> 00:43:25.170

Steven Mittelman (he/him), MD, PhD: And the fasting doesn't seem to work as consistently in these models which makes me wonder if fasting might help because it might have effects on the immune system.

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00:43:26.760 --> 00:43:34.410

Steven Mittelman (he/him), MD, PhD: So far, to date, as far as I'm aware, there are no clinical trials that looked at treatment outcome of fasting on cancer treatment.

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00:43:35.130 --> 00:43:45.030

Steven Mittelman (he/him), MD, PhD: but there have been several studies that have looked you know case series and such. And they show fewer toxicities and maybe improve quality of life. Just no outcome studies yet.

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00:43:47.670 --> 00:43:50.730

Steven Mittelman (he/him), MD, PhD: Caloric Restriction might be a little easier than fasting.

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00:43:51.930 --> 00:43:55.290

Steven Mittelman (he/him), MD, PhD: Again, there are preclinical studies showing reduce cancer incidence

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00:43:56.460 --> 00:44:03.480

Steven Mittelman (he/him), MD, PhD: but other than my study I haven't found any studies on caloric restriction and treatment efficacy. Sorry for the typo there.

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00:44:06.960 --> 00:44:15.420

Steven Mittelman (he/him), MD, PhD: And then, you know, a really interesting possibility would be to do some carb restriction or ketogenic diet.

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00:44:16.620 --> 00:44:27.000

Steven Mittelman (he/him), MD, PhD: This might be more tolerable in some patients and it also might take a take advantage of the fact that our host cells might have metabolic flexibility that cancer cells might not

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00:44:28.140 --> 00:44:43.650

Steven Mittelman (he/him), MD, PhD: There are some studies and preclinical models that show that it slows cancer growth and that it is synergistic in cancer treatment, but again, as far as I'm aware, there have been no rigorous clinical trials completed to date.

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00:44:47.010 --> 00:44:54.960

Steven Mittelman (he/him), MD, PhD: So based on this based on my finding which diet is best. And the answer is clearly, we don't know.

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00:44:56.100 --> 00:45:04.410

Steven Mittelman (he/him), MD, PhD: So, you know, it's really important for us to be using preclinical models because there's really the only way to start getting at the mechanism

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00:45:05.220 --> 00:45:17.730

Steven Mittelman (he/him), MD, PhD: of things, but we have to keep in mind that mice are not people. So as I alluded to earlier, most mice don't get fat on a high carb diet they get fat on a high fat diet

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00:45:18.150 --> 00:45:24.480

Steven Mittelman (he/him), MD, PhD: And that doesn't necessarily reflect human physiology. So putting a mouse that's

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00:45:25.410 --> 00:45:32.970

Steven Mittelman (he/him), MD, PhD: overweight/ obese, because they're on a 60% calories from fat diet and then changing over to a 10% from calories from fat diet

248

00:45:33.750 --> 00:45:40.620

Steven Mittelman (he/him), MD, PhD: doesn't in my mind mean that we should be addressing fat in humans. It might just be you know something completely...

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00:45:41.280 --> 00:45:46.500

Steven Mittelman (he/him), MD, PhD: It might have to do with the calories and might have to do with the metabolic shift. It might have to do with some hormonal

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00:45:47.010 --> 00:45:54.900

Steven Mittelman (he/him), MD, PhD: changes that occurred and so we have to take the mouse and rodent data with a big grain of salt or green of fat, if you will

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00:45:55.890 --> 00:46:11.820

Steven Mittelman (he/him), MD, PhD: and clinical trials are really the way to go. And there's even less information about exercise but exercise likely has beneficial effects as well, perhaps through caloric shift, perhaps through some of the same hormonal

252

00:46:14.130 --> 00:46:18.840

Steven Mittelman (he/him), MD, PhD: changes and perhaps through other mechanisms and so we need to study these things.

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00:46:19.950 --> 00:46:37.560

Steven Mittelman (he/him), MD, PhD: Unfortunately, as many of you are aware, dietary research is difficult and doing, you know, rigorous head to head comparisons of one diet versus another is very difficult because often you're changing, you know, many variables at the same time. And so

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00:46:39.180 --> 00:46:47.970

Steven Mittelman (he/him), MD, PhD: at the end of the day, you know, we had a modest diet that seemed to have a signal to improve leukemia outcome. And so we were happy to just stick with that diet because it works.

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00:46:48.300 --> 00:46:55.980

Steven Mittelman (he/him), MD, PhD: And then once we have something that's working. Perhaps you know we can start teasing apart specific nutrients or patterns that are most important.

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00:46:58.200 --> 00:47:05.580

Steven Mittelman (he/him), MD, PhD: Okay. So in summary, clearly obesity worsens acute leukemia outcome and getting an outcome from other cancers.

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00:47:06.240 --> 00:47:18.060

Steven Mittelman (he/him), MD, PhD: And I hopefully I can get you that fat cells protect leukemia cells through multiple mechanisms. The ones I are survivor signals, metabolic fuels and pharmacogenetics changes.

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00:47:19.620 --> 00:47:30.510

Steven Mittelman (he/him), MD, PhD: Lifestyle intervention improves leukemia outcome, I think, in mice and patients and diet and probably exercise clearly reduces cancer incidence

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00:47:31.080 --> 00:47:44.940

Steven Mittelman (he/him), MD, PhD: but also likely improves treatment outcome. So here's the article that just got published that again goes way more in depth into the literature for the preclinical and non clinical trials looking at diet in

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00:47:46.170 --> 00:47:47.130

Steven Mittelman (he/him), MD, PhD: cancer outcome.

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00:47:48.390 --> 00:48:02.820

Steven Mittelman (he/him), MD, PhD: But I think that's about it. This is just my acknowledgement. This is my lab and back when we used to be able to be together without masks in person. And of course, I'm really thrilled about my funding shown in the lower left.

262

00:48:03.840 --> 00:48:11.310

Steven Mittelman (he/him), MD, PhD: And I'd be happy to take any questions either now or somebody wants to email me, I'd be happy to answer.

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00:48:18.810 --> 00:48:25.740

Villanova Webinar 1: Okay. Thank you, Dr Mittelman for such a great presentation that is really getting

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00:48:27.150 --> 00:48:40.320

Villanova Webinar 1: getting to the core of what can we do to help our patients respond to chemo, even though some of it is preclinical. I think gets us thinking about

265

00:48:41.610 --> 00:48:49.410

Villanova Webinar 1: what wellness and well being looks like for someone who's undergoing cancer treatment.

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00:48:50.460 --> 00:48:54.420

Villanova Webinar 1: In a moment or two,

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00:48:56.280 --> 00:49:01.380

Villanova Webinar 1: we'll go ahead and take some questions. But first, I do want to remind everyone

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00:49:02.280 --> 00:49:11.310

Villanova Webinar 1: that if you've completed the webinar you will be emailed a link to an evaluation within a week. The email will be sent to the email address

269

00:49:11.970 --> 00:49:21.330

Villanova Webinar 1: that you used to register for the program. That evaluation will expire in three weeks so please complete it as soon as possible, just to ensure you receive your CE certificate quickly.

270

00:49:21.690 --> 00:49:39.450

Villanova Webinar 1: Once the evaluation is completed, a CE certificate will be emailed separately within about five business days. Remember, if you called into the webinar today please email us at cope@villanova.edu and provide your name, so that we can provide you with your CE certificate

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00:49:41.100 --> 00:49:44.010

Villanova Webinar 1: Just wanted to mention that we do have

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00:49:45.270 --> 00:49:53.790

Villanova Webinar 1: upcoming events, one of which you might be interested in is a presentation by Dr. Josiemer Mattei

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00:49:55.410 --> 00:50:04.800

Villanova Webinar 1: from the Harvard TH Chan School of Medicine. She will be talking about Mediterranean like diets for disease prevention in racial ethnic minority populations.

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00:50:05.250 --> 00:50:20.670

Villanova Webinar 1: That will be held on Wednesday, February 12 from 12 to 1pm Eastern Standard Time. So you can go ahead and visit the COPE website if you are interested and register for this free webinar. You will receive see credits for attending.

275

00:50:21.780 --> 00:50:28.020

Villanova Webinar 1: I wanted to mention that Fitzpatrick College of Nursing is thrilled to be studying the impact of COVID 19 on the healthcare workforce

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00:50:28.350 --> 00:50:32.310

Villanova Webinar 1: And to this end invites you to be a part of the nationwide CHAMPS study.

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00:50:32.700 --> 00:50:39.870

Villanova Webinar 1: If you or someone you know is a health professional, a first responder and essential worker or support staff in a hospital or nursing home,

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00:50:40.230 --> 00:50:52.290

Villanova Webinar 1: and are or did provide support for patients, treatments sites, or the community during the COVID-19 pandemic, you are encouraged to participate by completing a survey that takes about 15 minutes to complete.

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00:50:52.740 --> 00:51:03.090

Villanova Webinar 1: By hearing from these workers, we are hoping to better determine how we can improve services in the future. To find out more, you can visit the COPE website where you'll find a link to participate.

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00:51:04.650 --> 00:51:19.470

Villanova Webinar 1: We do offer an online catalog of webinars and presentations, which can provide you with 1 contact our or 1 CPEU so you can go to the website and search for topics of interest to you and that is another way that we

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00:51:20.880 --> 00:51:24.990

Villanova Webinar 1: hope that you will take advantage of other continuing education opportunities.

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00:51:26.250 --> 00:51:30.300

Villanova Webinar 1: Okay. And with that, we will go ahead. We do have some time for questions.

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00:51:32.160 --> 00:51:33.060

Villanova Webinar 1: And let's see.

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00:51:34.680 --> 00:51:41.730

Villanova Webinar 1: We do have a question. Dr Mittelman. Do you see increase in body fat and fat in the bone marrow in pediatric

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00:51:43.380 --> 00:51:46.770

Villanova Webinar 1: leukemia patients, even with weight loss during treatment?

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00:51:48.330 --> 00:52:04.980

Steven Mittelman (he/him), MD, PhD: Yeah, we do. I showed them a whole body fat. And you can see that at least in the ones who started out overweight or obese, we reduced that increase we prevented some of the increase in body fat, but the bone marrow still does become fatty, if you will.

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00:52:06.660 --> 00:52:18.060

Steven Mittelman (he/him), MD, PhD: Hopefully, you know, we don't know if reducing body fat accumulation is the key or is it the insulin sensitivity or is it the hormones, you know, we were trying to kind of go through for everything,

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00:52:19.410 --> 00:52:30.750

Steven Mittelman (he/him), MD, PhD: and so hopefully the statisticians can with the bigger trial tease apart which variable best predicted response to the intervention, so that we can then develop more targeted interventions.

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00:52:31.080 --> 00:52:48.480

Steven Mittelman (he/him), MD, PhD: If it's the body fat itself, then there are ways to try to look at that. If it's insulin sensitivity, then maybe something like metformin or exercise might actually be more beneficial than, you know, certain diets, or maybe a low carb diet might be, though, the way to go.

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00:52:49.920 --> 00:52:55.500

Villanova Webinar 1: Okay.And I was going to give a question of my own that I hope

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00:52:56.700 --> 00:53:07.320

Villanova Webinar 1: will be of interest to others. As I was listening to your there is checking body composition a routine part of determining

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00:53:07.890 --> 00:53:18.510

Villanova Webinar 1: chemo needs or in assessing let's say in children prior to the start of any kind of treatment. Is that assessed at all other than, you know, using the standard

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00:53:19.590 --> 00:53:21.810

Villanova Webinar 1: BMI measurements and that sort of thing.

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00:53:22.770 --> 00:53:30.030

Steven Mittelman (he/him), MD, PhD: No, I don't think it is routinely assessed. I mean, clearly. Yeah, you need to calculate a body surface area and wait for dosing

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00:53:31.080 --> 00:53:32.010

Steven Mittelman (he/him), MD, PhD: But I think

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00:53:33.180 --> 00:53:47.070

Steven Mittelman (he/him), MD, PhD: most oncology teams, they're focused on the chemo and the cancer and, you know, obesity is is not really at the forefront of their mind, for obvious reasons.

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00:53:47.910 --> 00:53:57.720

Steven Mittelman (he/him), MD, PhD: We're hoping that with more and more of this data, we can convince people that you know impacting the diet and the whole health of the individual might actually

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00:53:58.320 --> 00:54:16.470

Steven Mittelman (he/him), MD, PhD: improve outcome, and if so, yeah. Getting a nutrition consult, getting body composition, you know, addressing some of these things might be ways we can actually improve outcome without adding another chemotherapy or without going to bone marrow transplant or some of these other things.

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00:54:18.330 --> 00:54:36.000

Steven Mittelman (he/him), MD, PhD: And I didn't get into the data but BMI is really a poor surrogate for body composition during chemotherapy. I'm at the beginning, it's, it's a fair assessment, as I'm sure you're all aware with exceptions. It generally is somewhat proportional to body fat but

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00:54:37.710 --> 00:54:51.540

Steven Mittelman (he/him), MD, PhD: during treatment because these kids develop sarcopenic obesity, you can't just follow BMI. And so if you really want to do this, you do need some sort of assessment we use DEXA but it could be that at least getting a waist circumference or

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00:54:52.740 --> 00:54:57.150

Steven Mittelman (he/him), MD, PhD: caliper measurements or something would be better than just depending on BMI.

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00:54:58.380 --> 00:54:59.190

Steven Mittelman (he/him), MD, PhD: Yeah, okay.

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00:54:59.580 --> 00:55:12.690

Villanova Webinar 1: And a question about your ideals trial. Was there any measurement of the effect of the intervention on the children's mental or emotional health or body image, any of those psycho. Yeah, something

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00:55:13.560 --> 00:55:24.780

Steven Mittelman (he/him), MD, PhD: Great question. I think this might be one of the actual best benefits of the trial. Unfortunately, we didn't say assess it in t, so we couldn't look at it. But we're definitely going to include that.

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00:55:26.010 --> 00:55:32.580

Steven Mittelman (he/him), MD, PhD: You know my philosophy is if you, you know, when you have cancer or your family member or child has cancer,

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00:55:33.240 --> 00:55:44.610

Steven Mittelman (he/him), MD, PhD: you might feel pretty hopeless and you can't do much to affect that it's all in the doctors hands, but if you give the families, something they can do that can actually impact their outcome,

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00:55:45.090 --> 00:55:59.310

Steven Mittelman (he/him), MD, PhD: I think that might give them a sense of control that might help them deal with what you know is obviously a very horrible time in their life. So in the randomized trial we are getting quality of life measures, definitely.

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00:56:00.750 --> 00:56:13.770

Villanova Webinar 1: That's excellent. Okay, and then question on weight stigma and you mentioned it early on in your talk. What are your thoughts on this? Could you

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00:56:14.880 --> 00:56:20.760

Villanova Webinar 1: sort of, restate your thoughts on the role of weight stigma on the relationship between weight and cancer.

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00:56:22.110 --> 00:56:25.950

Villanova Webinar 1: And what can we as health professionals do to

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00:56:27.570 --> 00:56:30.990

Villanova Webinar 1: Reduce the impact of weight stigma on

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00:56:32.280 --> 00:56:44.520

Villanova Webinar 1: the likelihood of patients to get screened for cancer or to abide by any of the recommendations that might come by regarding dietary changes.

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00:56:44.700 --> 00:56:50.520

Steven Mittelman (he/him), MD, PhD: Well, I think, you know, obviously, the first step is being aware of and identifying it and

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00:56:50.880 --> 00:56:58.500

Steven Mittelman (he/him), MD, PhD: you know, it's just chilling to know that there are people who are you know dying from cancer that maybe wouldn't have if they felt more comfortable

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00:56:58.860 --> 00:57:10.410

Steven Mittelman (he/him), MD, PhD: going and seeing their doctor or if their doctor felt more comfortable doing the screening tests. So we really need to, you know, be aware of our own internal biases, so that we can

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00:57:11.010 --> 00:57:22.380

Steven Mittelman (he/him), MD, PhD: prevent them and you know it's a justice issue as far as I'm concerned, especially in these times, we really need to be to be aware of that.

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00:57:23.910 --> 00:57:32.070

Steven Mittelman (he/him), MD, PhD: I am sure that, you know, later diagnosis from not showing up because every time you go to the doctor, all they want to talk about is your weight.

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00:57:32.460 --> 00:57:43.140

Steven Mittelman (he/him), MD, PhD: And not you know anything else. I'm sure that's, you know, makes you not want to go to the doctor. So with my patients, you know, I tell them that weight is a number

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00:57:43.560 --> 00:57:46.470

Steven Mittelman (he/him), MD, PhD: And I don't really care about that number I care about their health.

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00:57:46.950 --> 00:57:56.160

Steven Mittelman (he/him), MD, PhD: And if they're metabolically healthy, then you know I recommend that they get exercise because that's healthy for everyone. I recommend they eat a vegetable once in a while because that's healthy

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00:57:56.970 --> 00:58:06.120

Steven Mittelman (he/him), MD, PhD: but I, you know, don't like to focus on their weight, certainly not at every visit because you know otherwise all you're doing is is just demoralizing them.

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00:58:07.980 --> 00:58:19.350

Steven Mittelman (he/him), MD, PhD: You know, if they're overweight and having a lot of metabolic issues from it, then you know we have to talk about that. But again, I just want them to be healthy. I don't necessarily want them to change their body size

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00:58:20.100 --> 00:58:26.010

Steven Mittelman (he/him), MD, PhD: to do that, so it's it's a difficult you know topic, as I'm sure all of you are aware

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00:58:27.120 --> 00:58:35.310

Steven Mittelman (he/him), MD, PhD: But the other thing is, you know, that's part of why it's so important for us to do some of this mechanistic work and see where the signal is because

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00:58:35.730 --> 00:58:47.430

Steven Mittelman (he/him), MD, PhD: If it is body fat percentage, then we need to address that body fat percentage. But if it's insulin sensitivity, there are ways to address it without weight loss per se or body fat loss per se.

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00:58:48.330 --> 00:58:57.030

Steven Mittelman (he/him), MD, PhD: So we really need to figure out where the signal is that we can target it now there's a chance because body weight affects so many things that it's multifactorial and

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00:58:57.510 --> 00:59:07.800

Steven Mittelman (he/him), MD, PhD: there's not going to be one signal and we need to kind of do a holistic approach to diet and exercise to get the most benefit, but I think we'll figure it out by doing more trials.

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00:59:09.090 --> 00:59:14.460

Villanova Webinar 1: Okay, and we have time for, I think, one more question, and that is, you know, there's a lot of

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00:59:15.600 --> 00:59:17.490

Villanova Webinar 1: burning interest in the

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00:59:18.750 --> 00:59:37.470

Villanova Webinar 1: minds of individuals who are exploring diets and we need to as health professionals respond to these questions and interest. And so the big question is, would you on a personal level advocate a keto diet for somebody who was undergoing

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00:59:38.580 --> 00:59:46.800

Villanova Webinar 1: chemo? I realize, you know, we have so much more to learn, but what's your, your gut reaction there too.

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00:59:47.100 --> 00:59:53.070

Steven Mittelman (he/him), MD, PhD: Yeah, that's tough. I certainly, you know, we don't normally recommend keto diet and kids.

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00:59:54.180 --> 01:00:01.410

Steven Mittelman (he/him), MD, PhD: Although you know in the older adolescent, if that you know I've always said the best diet is the one that the patient will adhere to.

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01:00:02.310 --> 01:00:12.750

Steven Mittelman (he/him), MD, PhD: So if they seem like they would respond to a keto diet, meaning you know they're not into the sweets and their problem is, you know, eating the just a ton of calories from other things,

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01:00:13.590 --> 01:00:24.210

Steven Mittelman (he/him), MD, PhD: Then I will, I will prescribe it to them, within reason, I would be hesitant to do this on a kid during chemotherapy, because I don't know

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01:00:24.720 --> 01:00:35.670

Steven Mittelman (he/him), MD, PhD: I don't know whether it will work or not. So it would be, you know, just my best guess. And at this point, we don't have much data, one way or the other. I, I don't see why it would hurt.

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01:00:37.350 --> 01:00:54.630

Steven Mittelman (he/him), MD, PhD: You know, one thing I should mention is, you know, leukemia is a bit unique because these kids don't get cachexia so much, at least not during the first phase. There are a lot of other cancers, especially in adults, where there's cachexia and you have to balance that with caloric balance.

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01:00:56.070 --> 01:01:04.470

Steven Mittelman (he/him), MD, PhD: And, you know, so I do think the goal is to and cachexia as a bad you know prognostic factor, obviously. So the goal is to address

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01:01:04.770 --> 01:01:18.840

Steven Mittelman (he/him), MD, PhD: what the problem is-insulin sensitivity, body fat while maintaining lean muscle mass and preventing cachexia as much as possible. How a ketogenic diet would play into that I just do not know. So I would I would hesitate at this point.

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01:01:19.920 --> 01:01:28.080

Villanova Webinar 1: Okay, thank you very much. I really appreciate you entertaining, these questions, especially those where, you know, there's not

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01:01:29.940 --> 01:01:40.080

Villanova Webinar 1: specific answers or guidance. So I really appreciate you just helping us understand what are the roadblocks, or what are the hesitations that go along with

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01:01:41.130 --> 01:01:44.760

Villanova Webinar 1: embarking on some of these dietary programs.

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01:01:45.420 --> 01:01:54.330

Villanova Webinar 1: So with that we are through for today. I would encourage all our listeners to make sure you fill out the evaluation and submit that so you can get your CE certificate

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01:01:54.720 --> 01:02:07.680

Villanova Webinar 1: And Dr. middlemen. Thank you so much in this very, very busy time you your attendance here is just so greatly appreciated by all of us. So best of health to you and and good luck with your research.

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01:02:07.950 --> 01:02:12.090

Steven Mittelman (he/him), MD, PhD: My pleasure. Thank you for the opportunity. Stay safe and healthy. everybody.

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01:02:12.210 --> 01:02:13.200

Villanova Webinar 1: Take care. Bye bye.