Impact of Exercise and Nutrition on Cancer Treatment-Related Outcomes

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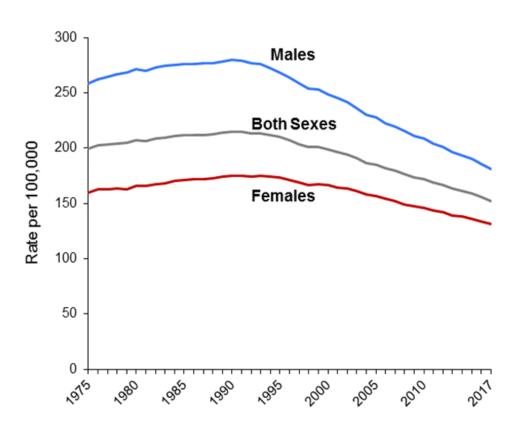






Cancer Mortality Rates in the United States have decreased by 30% since 1990

Trends in Cancer Death Rates* by Sex, US, 1975-2017



- Treatment advances have contributed to decreased cancer mortality rates.
- Completion of treatment is critical to improve outcomes.

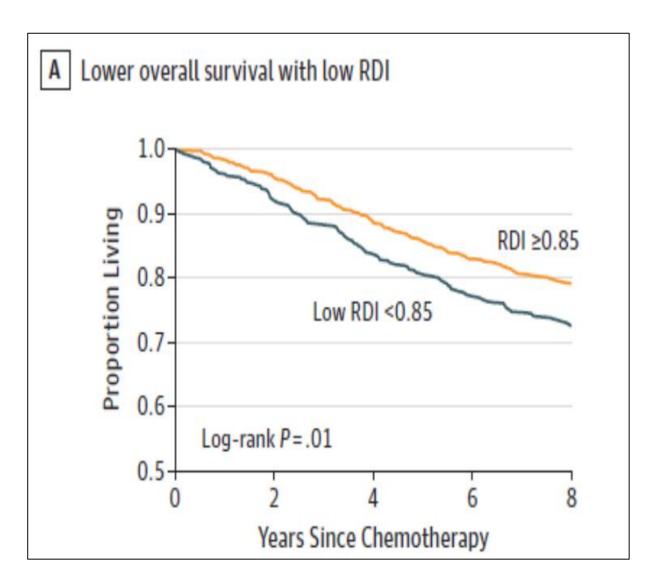
*Age-adjusted to the 2000 US standard population.
Source: National Center for Health Statistics, Centers for Disease Control and Prevention, 2019.

Adherence to Chemotherapy is Important

- Relative dose intensity (RDI) is a measure of chemotherapy completion:
 - chemotherapy <u>delivered</u> / chemotherapy <u>prescribed</u>, accounting for dose intensity and duration of drugs.
- An RDI <85% is a common clinical threshold whereby chemotherapy effectiveness and prognosis significantly worsen.
- Observational studies in breast cancer have shown wide ranges of RDI

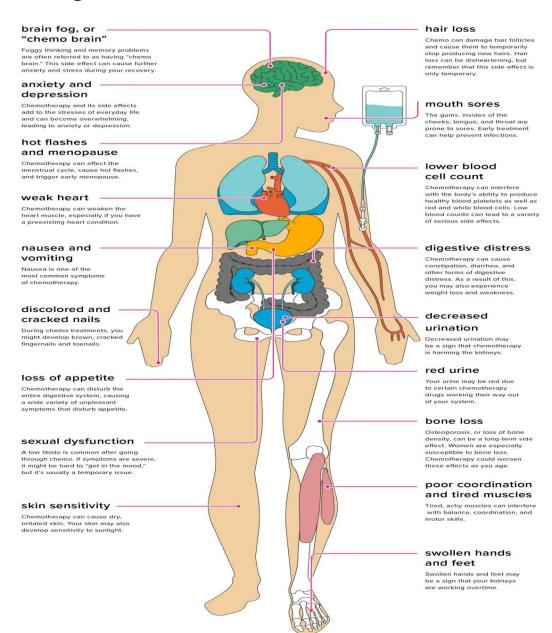
Average RDI: 74% to 88% RDI < 85%: 24% to 55% Dose reductions \geq 15%: 24% to 36% Dose delays > 7 days: 25% to 31%

- Predictors of reduced RDI included:
 - chemotoxicity
 - advanced age
 - greater BSA
 - anthracycline-based regimens
 - comorbidities



Chemotherapy Toxicity and Treatment Adherence

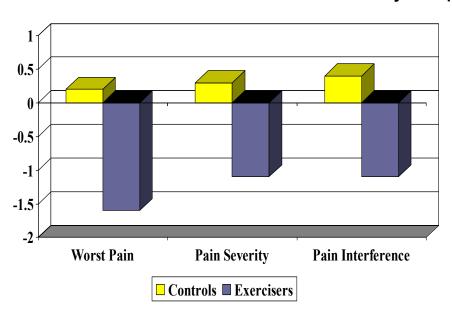




Exercise reduces treatment-related toxicities

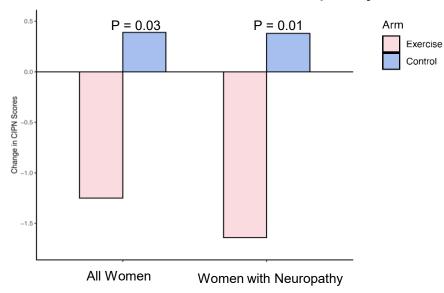


Exercise reduces treatment-related joint pain



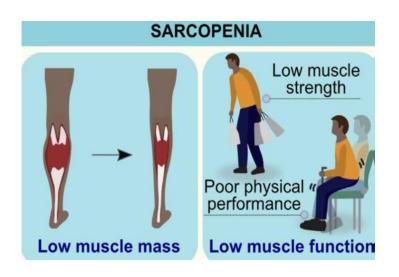


Exercise reduces neuropathy



Irwin et al. JCO. 2015

Sarcopenia and Muscle Loss



Prevalence of sarcopenia in patients with cancer according to the primary tumor location in the literature (all stages)

Primary cancer	Stage [reference]	% With sarcopenia, median (range, %)
Colorectal	Stage I–IV [20,34,53–69]	49 (20-80)
Esophagus	Stage I-IV [54,70-80]	53 (16-75)
Gastric	Stage I–IV [81–86]	47 (23-70)
Lung	Stage I–IV [42–45]	70 (47-79)
Kidney	Stage I–IV [87–94]	53 (29-90)
Pancreatic	Stage I–IV [16,41,46–52]	56 (44-89)
Liver	Stage I–IV [95–99]	54 (28-76)
Breast	Stage I–IV [100–106]	38 (14-67)
Ovarian	Stage I–IV [39,107,108]	47 (45-50)
Melanoma	Stage I–IV [35,109]	44 (24-63)
Bladder	Stage I-IV [110-114]	48 (33-69)
Prostate	Stage I–IV [115,116]	52 (47-56)
Head & neck	Stage I–IV [117]	64
Lymphoma	Stage I–IV [118–120]	51 (47-55)
Mixed	Stage I–IV [29,31,38,121–122]	4 (15–4)



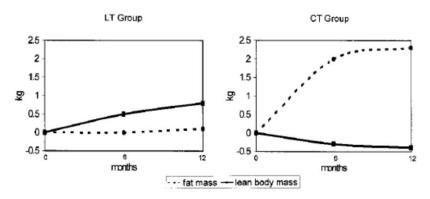


Fig 5. Change in fat mass and lean body mass from baseline by group.

Exercise and Chemotherapy Completion

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Effects of Aerobic and Resistance Exercise in Breast Cancer Patients Receiving Adjuvant Chemotherapy: A Multicenter Randomized Controlled Trial

Kerry S. Courneya, Roanne J. Segal, John R. Mackey, Karen Gelmon, Robert D. Reid, Christine M. Friedenreich, Aliya B. Ladha, Caroline Proulx, Jeffrey K.H. Vallance, Kirstin Lane, Yutaka Yasui, and Donald C. McKenzie

From the University of Alberta; Cross Cancer Institute, Edmonton; Alberta Cancer Board, Calgary, Alberta; Ottawa

VOLUME 33 - NUMBER 17 - JUNE 10 2015

7

ORIGINAL REPORT

JOURNAL OF CLINICAL ONCOLOGY

Effect of Low-Intensity Physical Activity and Moderate- to High-Intensity Physical Exercise During Adjuvant Chemotherapy on Physical Fitness, Fatigue, and Chemotherapy Completion Rates: Results of the PACES Randomized Clinical Trial

Hanna van Waart, Martijn M. Stuiver, Wirn H. van Harten, Jacobien M. Kieffer, Marianne de Maaker-Berkhof, Gabe S. Sonke, Hanna van Waart, Martijn M. Stuiver, Wim H. van Harten, Edwin Geleijn, Jacobien M. Kieffer, Laurien M. Buffart, Marianne de Maaker-Berkhof, Epie Boven, Jolanda Schrama, Maud M. Geenen, Jetske M. Meerum Terwogt, Aart van Bochove, Vera Lustig, Simone M. van den Heiligenberg, Carolien H. Smorenburg, Jeannette A.J.H. Hellendoorn-van Vreeswijk, Gabe S. Sonke, and Neil K. Aaronson



Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintria



Recruitment strategies and design considerations in a trial of resistance training to prevent dose-limiting toxicities in colon cancer patients undergoing chemotherapy

Bette J. Caan ^{a, *}, Jeffrey A. Meyerhardt ^b, Justin C. Brown ^c, Kristin L. Campbell ^d, Elizabeth M. Cespedes Feliciano ^a, Catherine Lee ^a, Michelle C. Ross ^a, Sara Quinney ^e, Charles Quesenberry ^a, Barbara Sternfeld ^a, Kathryn H. Schmitz ^f

- Courneya et al JCO 2007:
 - RDI:
 - UC (84.1%)
 - AET (87.4%)
 - RET (89.8%)*
 - % received ≥ 85% RDI:
 - UC (65.9%)
 - AET (74.4%)
 - RET (78.0%)*
- van Waart et al JCO 2015:
 - Chemotherapy dose adjustments:
 - UC (34%)
 - Onco-Move (34%)
 - OnTrack (12%)*
 - Average dose reduction:
 - UC (25%)
 - Onco-Move (10%)*
 - OnTrack (10%)*

 Caan B et al. FORCE Trial of RT with RDI as the primary end point in patients with colon cancer.

Bland K et al. Crit Rev Oncol Hematol 136:79-85. 2019

^a Division of Research, Kaiser Permanente Northern California, 2000 Broadway, Oakland, CA 94612, USA

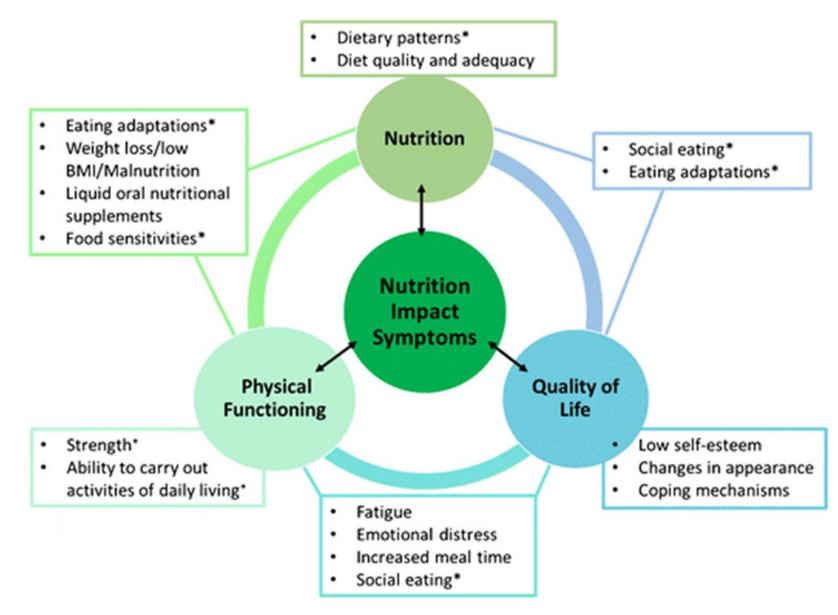
b Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, 450 Brookline Ave, Boston, MA 02215, USA

^c Cancer Metabolism Research Program, Pennington Biomedical Research Center, Louisiana State University, 6400 Perkins Road, Baton Rouge, Louisiana 70808, USA
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Disease and Therapeutic Response Modeling Program, Indiana University School of Medicine, 950 W Walnut Street, Indianapolis, Indiana 46202, USA Penn State Cancer Institute, The Pennsylvania State University, 500 University Drive, Hershey, PA 17033, USA

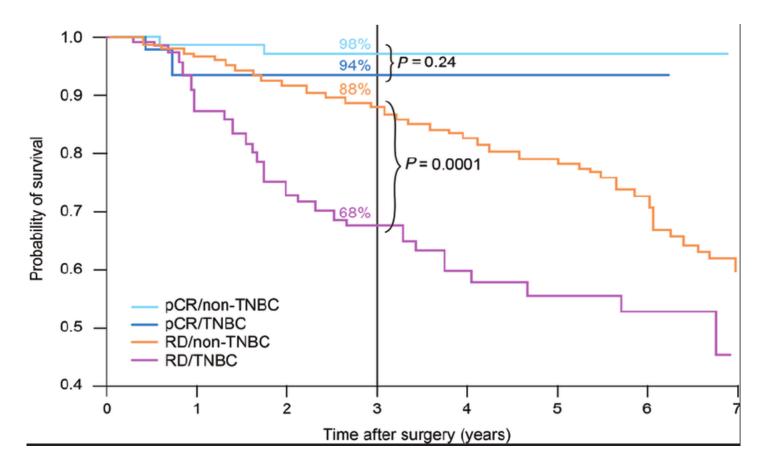
Chemotherapy and Nutrition Impact Symptoms (PRO-CTCAE)

- Nutrition impact symptoms
 (NIS), such as fatigue, nausea,
 vomiting, oral mucositis,
 dysphagia, xerostomia, and
 decreased appetite, make it
 difficult to eat well, potentially
 affecting chemotherapy
 completion.
- ~80% of women with breast cancer have at least one NIS at 1 month after starting chemotherapy.
- Dietary interventions during cancer treatment are limited and, to our knowledge, there are no published diet trials on RDI as a primary end point.



Pathologic Complete Response

- Pathologic complete response (pCR), defined as disappearance of all invasive cancer in the breast after completion of neoadjuvant chemotherapy, is an important prognostic measure.
- We are not aware of any trials of exercise and/or diet on pCR in patients with breast cancer.



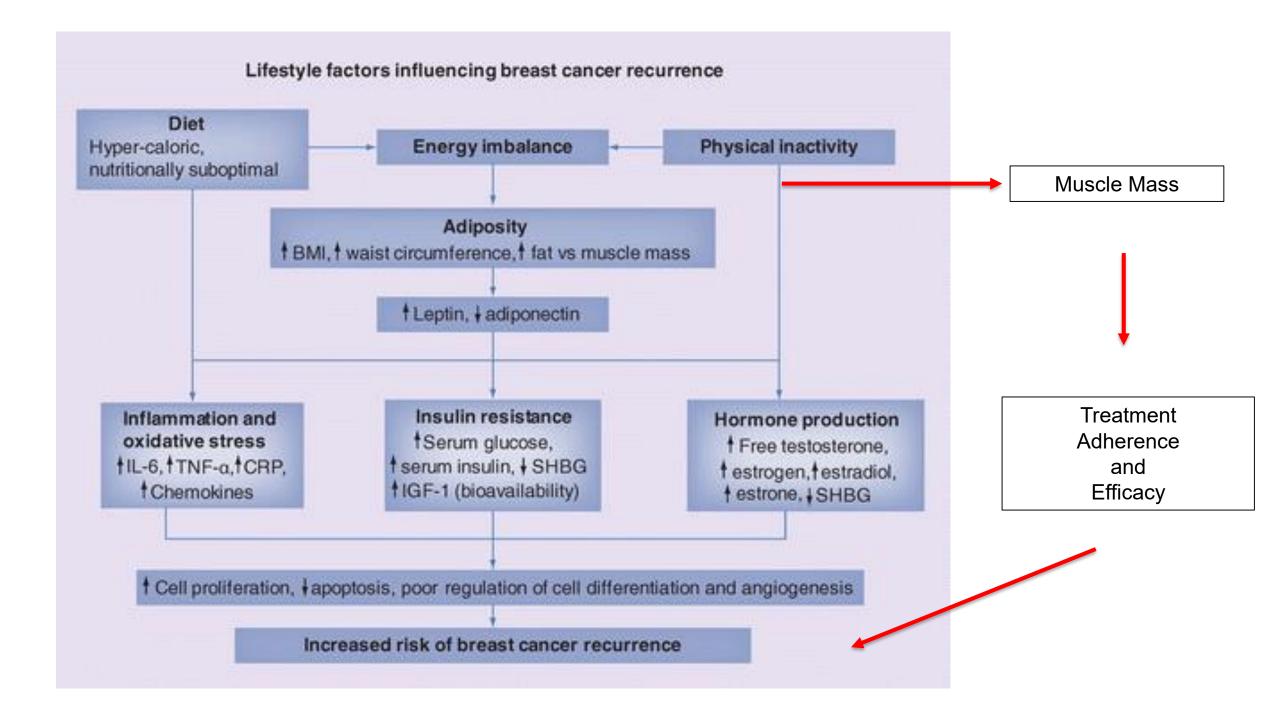
Imagine if there was a therapy that could:

- Increase muscle mass and reduce adiposity
- Reduce nutrition impact symptoms
- Reduce other treatment toxicities
- Increase treatment adherence
- Improve quality of life
- Extend overall survival?



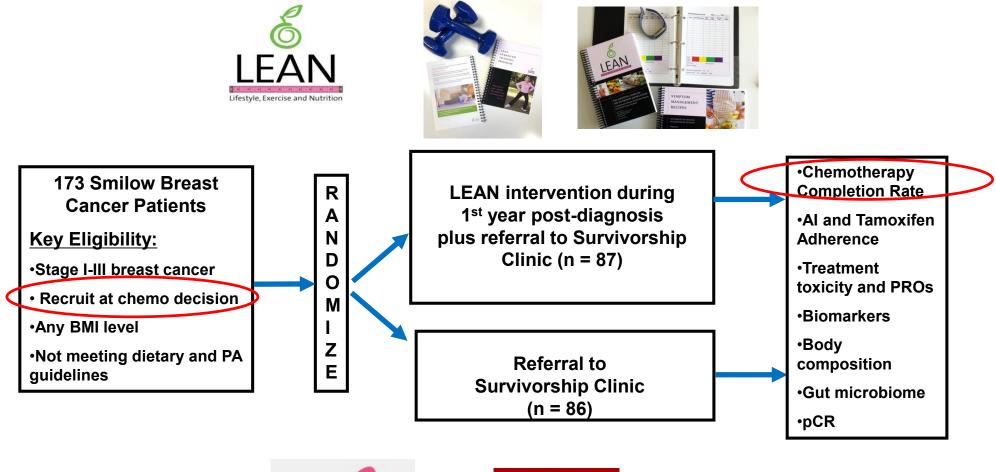






Lifestyle, Exercise and Nutrition (LEAN) trial EaRly after diagnosis (LEANer)

Pls: Tara Sanft and Melinda Irwin NCI R01CA207753



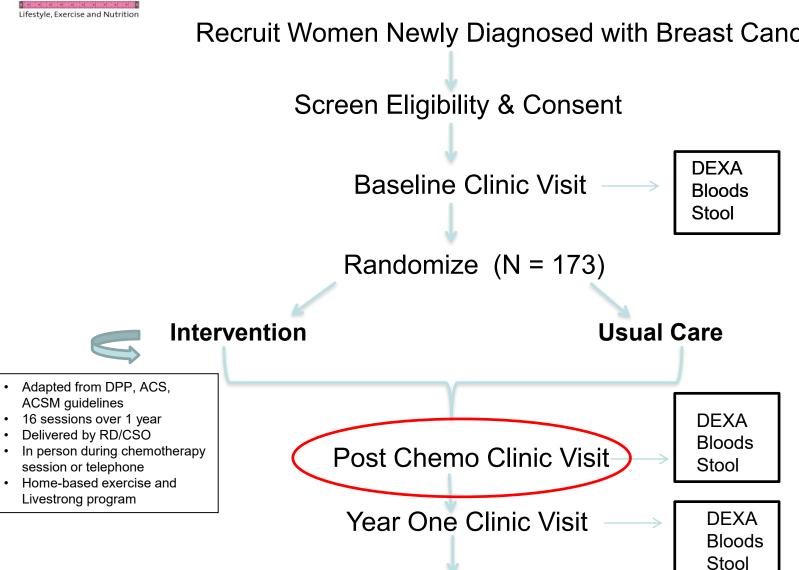






Study Design

Recruit Women Newly Diagnosed with Breast Cancer



Year Two Clinic Visit

Urine

Lifestyle, Exercise and Nutrition (LEAN) trial <u>EaRly</u> after diagnosis (LEANer)

Tara Sanft

Melinda Irwin

Leah Ferrucci

Brenda Cartmel

Maura Harrigan

Courtney McGowan

Michelle Zupa

Fangyong Li

Lingeng Lu

Leah Puklin

Anlan Cao

Thai Nguyen

Margaret Pichardo

Andrea Silber

Beth Jones

Anees Chagpar

Tish Knobf

Jennifer Ligibel (DFCI)

Marian Neuhouser (Fred Hutch)

Dawn Hershman (Columbia)

Karen Basen-Engquist (MD Anderson)









Study Groups

Nutrition & Exercise Intervention Group

- Delivered by Registered Dietitian-Certified Specialist in Oncology (RD, CSO)
- 16, 30-minute counseling sessions over the first year
- Conducted in-person during chemo session, telephone and/or via zoom

Usual Care/Control Groups

- Consult with Smilow Cancer Hospital RD upon request
- One 60-min counseling session at end of the study
- Referral to Survivorship Clinic





Nutrition Intervention

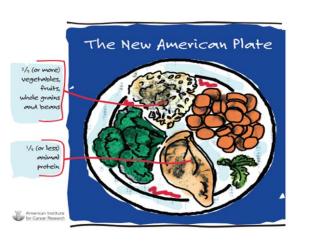
Protocol adapted from DPP, 2015 Dietary Guidelines, AICR, ACS, ACSM

Nutrition Goals

- ≥5 servings of vegetables + fruits per day
- ≥ 25 grams of fiber per day
- 1.5g/kg body weight protein per day
- <30 grams of added sugar per day
- ≤ 18 ounces/wk of processed/red meat

Nutrition Education

- Limit alcohol
- Drink 64 oz water per day
- Dietary fat ≤ 25%
- 2-3 servings fish/week
- <2300 mg sodium per day
- Reduce dietary supplement use
- Implement food safety practices









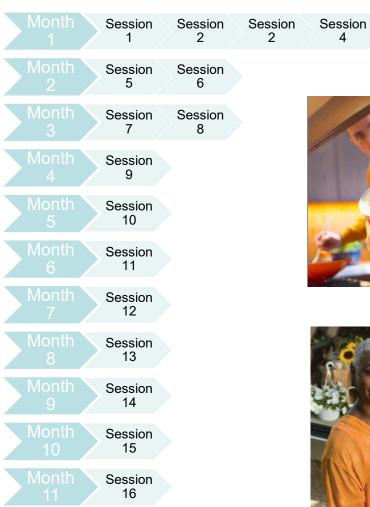


Physical Activity Intervention

- 150 min/wk moderate-intensity exercise or 75 min/wk of vigorousintensity exercise
- 2x/week strength training
 - Home set of dumbbells
 - Home-based, LEAN videos online
 - Livestrong Program at YMCA
- Fitbit 10,000 steps/day
- Breaks from sitting



LEANer Intervention Counseling Sessions







Sessions 1-4

- Establish Exercise Baseline
- Nutrition Skill Building
- Food Safety
- Managing Side Effects
- •LEAN Recipe book developed specifically for this study
- •Daily Log: food exercise side effects

Sessions 5 - 11

- Progressive Exercise Goals
- •Mindful Eating Practices
- •Food Shopping/Dining Out
- Work/Travel Adaptations

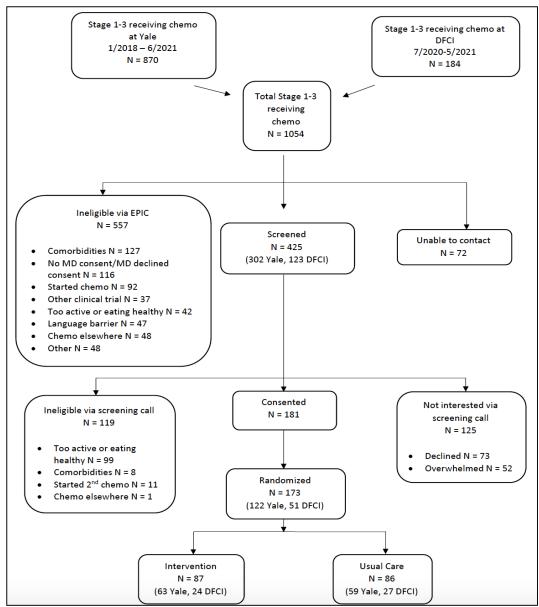
Sessions 12 - 16

- Survivorship Issues
- Late Effects of Treatment
- Sustaining Lifestyle Changes

Statistical Power and Sample Size

Estimated sample size of 86 subjects per arm (n=172) will achieve 90% power to detect a 5% difference in RDI between two arms at significance level of 0.05

Consort Diagram



Recruitment Summary

- 1,054 women scheduled to receive chemotherapy
- 557 were ineligible via EMR
- 425 screening calls completed
- 306 women were eligible
- 173 Enrolled (57% of those eligible)

Primary reasons for ineligibility:

- PA>150 min/wk
- physical limitation
- Comorbidities
- not English-speaking

Baseline Characteristics

Table 2. Baseline Characteristics of the LEANer study (N = 173)			
	Treatment group		
	Intervention (N = 87)	<i>Usual care</i> (N = 86)	
Age (years), Mean (SD)	52.32 (11.30)	53.29 (10.92)	
Race/Ethnicity			
Asian or Pacific Islander	2 (2.30%)	4 (4.65%)	
Black or AA	11 (12.64%)	14 (16.28%)	
Hispanic	8 (9.20%)	5 (5.81%)	
Non-Hispanic White	60 (68.97%)	59 (68.60%)	
Other	6 (6.90%)	4 (4.65%)	
Marital status			
Divorced/separated/ widowed/never married	28 (32.18%)	27 (32.14%)	
Married or living with a partner	59 (67.82%)	57 (67.86%)	
Health insurance			
Medicare or Medicaid	14 (16.09%)	17 (19.77%)	
Other	23 (26.44%)	24 (27.91%)	
Private insurance	50 (57.47%)	45 (52.33%)	
Postmenopausal	48 (55.14%)	46 (54.11%)	
Education			
College and above	58 (67.44%)	50 (58.14%)	
Less than college	28 (32.56%)	36 (41.86%)	
Number of chemotherapy cycles			
4	23 (26.44%)	25 (29.07%)	
> 4	64 (73.56%)	61 (70.93%)	
ER/PR positive	59 (67.82%)	59 (68.60%)	
HER2 positive	15 (17.24%)	15 (17.44%)	
Chemotherapy			
Neoadjuvant	41 (47.13%)	33 (38.37%)	
Adjuvant	46 (52.87%)	53 (61.63%)	

Summary

- Average age 53 (+/-11)
- Average BMI = $29.7 \pm 6.8 \text{ kg/m}^2$
- 55% postmenopausal
- 22% URM
- 51% Stage I
- 72% had ≥ 4 cycles of chemo
- N = 73 of 173 had neoadjuvant chemotherapy
- Impact of COVID-19:
 - N = 70 completed chemo prior to March 2020
 - After March 2020, more short chemo courses prescribed (i.e., TC x4)
 - Not able to collect blood and DEXA

27 Different Chemotherapy Regimens

		Number of patients
Chemo Regimen	Number of cycles	(N = 173)
70% of all prescribed in	regimens	
DDAC -> TAXOL	>4	41
TC x4	4	46 (20 DFCI)
DDAC -> DDTAXOL	>4	35 (18 DFCI)
23% of all prescribed	regimens	
TAXOL -> DDAC	>4	8
TCHP	>4	6 (1 DFCI)
DDAC -> TAXOL+CARBO (Carbo q21 days)	>4	4
DDAC -> TAXOL+CARBO (weekly)	>4	2
DDAC -> THP	>4	5
THP	>4	9 (9 DFCI)
TAXOL + HERCEPTIN	>4	5
7% of all prescribed	regimens	
MEDI + ABRAXANE -> DDAC + MEDI	>4	2
THP -> DDAC (Herceptin + Perjeta x4 q21 days)	>4	2 (1 DFCI)
THP -> DDAC (Taxol + Herceptin weekly + Perjeta q21 days)	>4	1
TAXOL + CARBO -> DDAC	>4	1
CMF	>4	1
TCH x4	4	1 (1 DFCI)
TCH	>4	1
SGN-LIV1A -> DDAC (ISPY)	>4	1
ABRAXANE + PEMBROLIZUMAB	>4	1 (1 DFCI)
DDAC + PEMBROLIZUMAB -> TAXOL + CARBO + PEMBRO	>4	1

AC =
Adriamycin/Cytoxan
T= Paclitaxel or
Docetaxel
Carbo= Carboplatin
H= Trastuzumab
P= Pertuzumab

Adherence to Intervention during Chemotherapy

Intervention - 16 Sessions over the 1-year intervention period

Avg # sessions during chemotherapy = 8

Percent of planned sessions completed during chemotherapy:

79 of 87 women completed 100% expected sessions

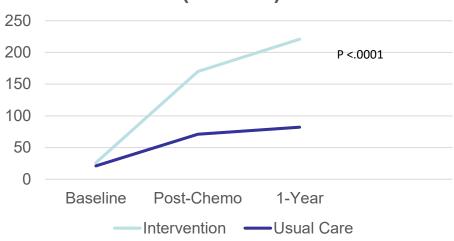
2 completed >60%

4 completed <40%

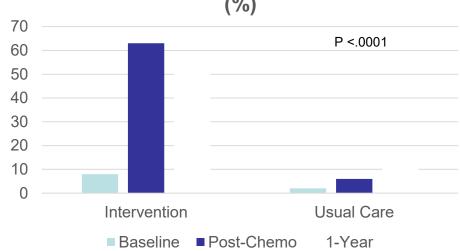
Intervention group significantly improved healthy behaviors

Variable	Baseline (n=173)	Change at End of Chemotherapy Intervention (n=87)	Change at End of Chemotherapy Usual Care (n=86)	P-Value
Dhysical Astivity	07 144	Mean <u>+</u> SD	Mean <u>+</u> SD	0.004
Physical Activity (min/wk)	27 <u>+</u> 41	143 <u>+</u> 120	48 <u>+</u> 100	0.001
Resistance Training	4%	71%	7%	0.0001
Fruit + Vegetable (servings/day)	4.2 <u>+</u> 2.4	0.8 <u>+</u> 2.5	-0.2 <u>+</u> 2.0	0.01
Fiber (g/day)	18.4 <u>+</u> 8.0	0.7 <u>+</u> 7.8	-3.1 <u>+</u> 8.1	0.007
Healty Eating Index 2015 (points)	67.1 <u>+</u> 9.7	4.7 <u>+</u> 11.0	1.7 <u>+</u> 9.0	0.09

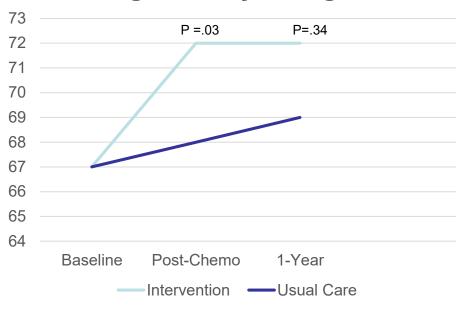
Average Physical Activity (min/wk)



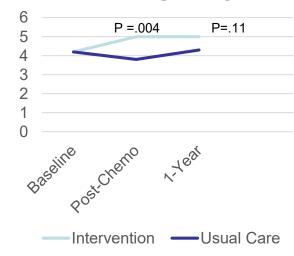
2+ Resistance Training Per Week (%)



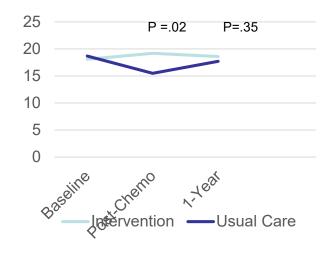
Average Healthy Eating Index



Average FV Servings/Day



Average Fiber (Grams/Day)



PRO-CTCAE Symptoms

	N (%) with Mild+ Symptoms (Grade 1 to 4) ²			N (%) with Severe+ Symptoms (Grade 3 and 4)		
PRO-CTCAE Symptom (Nutrition Impact Symptoms)	Intervention N=82	Usual Care N=74	P-value	Intervention N=82	Usual Care N=74	P-value
Severity of dry mouth	46 (56%)	44 (60%)	0.67	14 (17%)	14 (19%)	0.76
Severity of difficulty swallowing	23 (28%)	20 (27%)	0.89	2 (2%)	6 (8%)	0.11
Severity of mouth/throat sores	31 (38%)	30 (41%)	0.73	4 (5%)	5 (7%)	0.62
Interference of mouth/throat sores	15 (18%)	19 (26%)	0.26	1 (1%)	5 (7%)	0.07
Severity of problems with tasting	58 (71%)	52 (70%)	0.95	17 (21%)	16 (22%)	0.89
Severity of decreased appetite	39 (48%)	39 (53%)	0.52	14 (17%)	7 (10%)	0.16
Interference of decreased appetite	24 (29%)	27 (37%)	0.34	7 (9%)	7 (10%)	0.84
Frequency of nausea	41 (50%)	28 (38%)	0.13	10 (12%)	7 (10%)	0.58
Severity of nausea	40 (49%)	21 (28%)	0.009	8 (10%)	5 (7%)	0.50
Frequency of vomiting	10 (12%)	5 (7%)	0.25	0 (0%)	0 (0%)	1.00
Severity of vomiting	8 (10%)	6 (8%)	0.72	1 (1%)	2 (3%)	0.50
Frequency of heartburn	41 (50%)	37 (50%)	1.00	13 (16%)	13 (18%)	0.77
Severity of heartburn	34 (42%)	31 (42%)	0.96	8 (10%)	7 (10%)	0.95
Severity of constipation	32 (40%)	25 (34%)	0.50	12 (15%)	9 (12%)	0.65
Frequency of diarrhea	41 (50%)	33 (45%)	0.50	13 (16%)	12 (16%)	0.95

¹Adjusted for baseline PRO-CTCAE value

² PRO-CTCAE scoring: 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe

PRO-CTCAE Symptoms

		N (%) with Mild+ Symptoms (Grade 1 to 4) ²			N (%) with Severe+ Symp (Grade 3 and 4)		•
PRO-CTCAE Sympton (Nutrition Impact Sym						P-value	
Severity of dry mouth		46 (56%)	44 (60%)	0.67	14 (17%)	14 (19%)	0.76
Severity of difficulty s	wallowing	23 (28%)	20 (27%)	0.89	2 (2%)	6 (8%)	0.11
Severity of mouth/thro	oat sores	31 (38%)	30 (41%)	0.73	4 (5%)	5 (7%)	0.62
Interference of mouth							0.07
Severity of problems	Interv	Intervention group was able to increase diet				diet	0.89
Severity of decreased		•					0.16
Interference of decrea	quality e	<mark>ven while e</mark>	xperiend	cing tre	eatment-l	related	0.84
Frequency of nausea			<mark>sympton</mark>	1 S			0.58
Severity of nausea							0.50
Frequency of vomiting	9	10 (12%)	5 (7%)	0.25	0 (0%)	0 (0%)	1.00
Severity of vomiting		8 (10%)	6 (8%)	0.72	1 (1%)	2 (3%)	0.50
Francisco of boorthis	rn 41 (50%) 37 (50%) 1.00 13 (16%) 13 (18%)				13 (18%)	0.50	
Frequency of heartbu	•	` '		34 (42%) 31 (42%) 0.96 8 (10%) 7 (10%)			0.77
Severity of heartburn		34 (42%)	31 (42%)	0.96	8 (10%)	` ,	
		34 (42%) 32 (40%)	31 (42%) 25 (34%)	0.96 0.50	8 (10%) 12 (15%)	` ,	0.77

¹Adjusted for baseline PRO-CTCAE value

² PRO-CTCAE scoring: 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe

Effect of LEANer Intervention on Chemotherapy Adherence

Variable	Intervention (n=87) Mean <u>+</u> SD or N (%)	Usual Care (n=86) Mean <u>+</u> SD or N (%)	P-Value
RDI continuous	92.9% <u>+</u> 12.1%	93.6% <u>+</u> 11.1%	0.69
RDI < 85%	17 (19.5%)	13 (15.1%)	0.44
Dose Reductions	25 (29%)	24 (28%)	0.96
Toxicity Dose Delays (≥5 days)	18 (21%)	18 (21%)	0.90
Dose Reductions and/or Delays	33 (38%)	31 (36%)	0.80

Reasons for Chemotherapy Dose Reductions and/or Delays (reported in EPIC)

Reason	Intervention (n=33)	Usual Care (n=31)	
Neuropathy	16 (48%)	17 (55%)	
Infections	8 (24%)	7 (23%)	
Hematologic Toxicities	9 (27%)	8 (26%)	
Mouth Sores	3 (10%)	1 (3%)	
Diarrhea	1 (3%)	1 (3%)	
Constipation	2 (6%)	0 (0%)	
Dehydration	1 (3%)	1 (3%)	
Nausea/Vomiting	1 (3%)	0 (0%)	
Fatigue	1 (3%)	1 (3%)	
Transaminases	1 (3%)	3 (10%)	
Skin Toxicities	1 (3%)	2 (6%)	
Immune-related Toxicities	0 (0%)	2 (6%)	
Other	1 (3%)	5 (16%)	

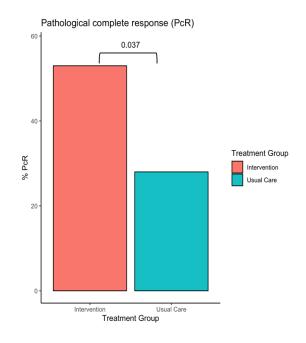
Individual participants could have more than one reason for dose reduction and/or delay.

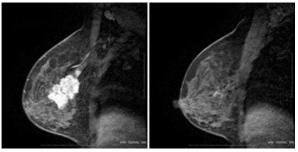
Other reasons: edema, depression, tachycardia, expander replacement surgery, appendectomy, and unspecified fever

Effect of LEANer Intervention on Pathologic Complete Response

Variable	Intervention (n=40) N (%)	Usual Care (n=32) N (%)	P- Value
Pathologic Complete Response	21/40 (53%)	9/32 (28%)	0.037
RDI Continuous	92.0% ± 12.1%	89.3% ± 11.6%	0.34
Dose Reductions and/or	20 (50%)	19 (63%)	0.43
Delays			

Improved diet quality and exercise might have direct effects on tumor response via improved metabolic, inflammatory and immune function, rather than via chemotherapy completion.





Higher BMI is associated with 32% Lower Odds of Pathologic Complete Response

Author(s) and Year			Odds Ratio [95% CI]	
			:	
Study 1	Litton	2008		0.78 [0.49, 1.24]
Study 2	Fontanella	2015	•=•	0.64 [0.56, 0.74]
Study 3	Elsamany	2015	:	0.24 [0.10, 0.58]
Study 4	Karatas	2016		0.34 [0.13, 0.89]
Study 5	Del Fabbro	2012		1.03 [0.44, 2.41]
Study 6	Lee	2012		0.52 [0.07, 3.86]
Study 7	lwase	2014		1.68 [0.25, 11.42]
Study 8	Warner	2016	⊢= +	0.73 [0.61, 0.88]
Study 9	Eralp	2009		1.22 [0.24, 6.29]
Study 10	Erbes	2015	· · · · · · · · · · · · · · · · · · ·	0.68 [0.28, 1.65]
Study 11	Kogawa	2018		1.00 [0.56, 1.81]
RE Model(Q = 12.	97, df = 9, p = 0.23; I^2 =	4.0%)	•	0.68 [0.61, 0.77]
			0.25 1 2	
			Odds Ratio	Wang at all Bro

Wang et al. Breast Cancer 2021

Impact of a Pre-Operative Exercise Intervention on Breast Cancer Proliferation and Gene Expression: Results from the Pre-Operative Health and Body (PreHAB) Study



Jennifer A. Ligibel¹, Deborah Dillon², Anita Giobbie-Hurder³, Anne McTiernan⁴, Elizabeth Frank¹, MacIntosh Cornwell¹, Matthew Pun¹, Nancy Campbell¹, Ryan J.O. Dowling⁵, Martin C. Chang⁶, Sara Tolaney¹, Anees B. Chagpar⁷, Rachel L. Yung⁸, Rachel A. Freedman¹, Laura S. Dominici⁹, Mehra Golshan⁹, Esther Rhei⁹, Krishan Taneja², Ying Huang¹⁰, Myles Brown¹, Eric P. Winer¹, Rinath Jeselsohn¹, and Melinda L. Irwin¹¹

npj Breast Cancer

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ARTICLE OPEN



Impact of a randomized weight loss trial on breast tissue markers in breast cancer survivors

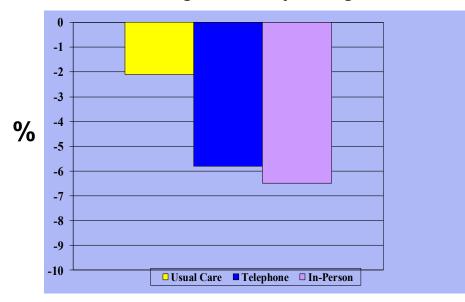
Christina M. Dieli-Conwright [o] ^{1 ⊠}, Maura Harrigan², Brenda Cartmel^{2,3}, Anees Chagpar^{3,4}, Yalai Bai⁴, Fang-yong Li [o], David L. Rimm [o], Lajos Pusztai [o], Lingeng Lu [o], Tara Sanft^{3,4} and Melinda L. Irwin^{2,3}



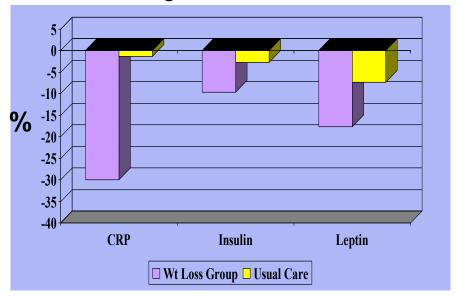
Randomized Trial Comparing Telephone Versus In-Person Weight Loss Counseling on Body Composition and Circulating Biomarkers in Women Treated for Breast Cancer: The Lifestyle, Exercise, and Nutrition (LEAN) Study

Maura Harrigan, Brenda Cartmel, Erikka Loftfield, Tara Sanft, Anees B. Chagpar, Yang Zhou, Mary Playdon, Fangyong Li, and Melinda L. Irwin

%Change in Body Weight



% Change in Biomarkers



RCT of Diet and Exercise in 439 Postmenopausal Women

	Diet	Exercise	Diet + Exercise
Insulin	-22.3%	-7.8%	-24.3%
Glucose	-2.4%	-0.9%	-2.8%
HOMA IR	-24.3%	-8.6%	-26.4%
Estrone	-9.6%	-5.5%	-11.1%
Estradiol - total - free	-16.2% -21.4%	-4.9% -4.7%	-20.3% -26.0%
SHBG	+22.4%	-0.7%	+25.8%
Testosterone	-0.9%	-4.9%	-5.9%
Leptin	-27.1%	-12.7%	-40.1%
Adiponectin	+9.5%		+6.6%
hsCRP	-36.1%	-8.5%	-41.7%
IL-6	-23.1%	-4.5%	-24.3%



Anne McTiernan

"Real life" value of the LEANer intervention



- "I am physically stronger now than before my diagnosis."
- "It never have occurred to me to be active and pay attention to eating habits during treatment."
- "I've completely changed everything I was doing with food and exercise."
- "I wasn't sure what to expect when I started the study but now I know it was life-saving to me."



Strengths and Limitations

Limitations

- High variance in regimens
- COVID led to unanticipated changes in regimen dosing but remote intervention allowed continuance of study
- Restricted to Englishspeaking only

Strengths

- Generalizable to a "real world" setting
- Higher URM enrollment compared to other lifestyle studies
- RDI collected and verified in real time

Analysis is forthcoming of 1-year and 2-year outcomes (endocrine therapy adherence, PROs, body composition, and biomarkers)

LEANer Summary



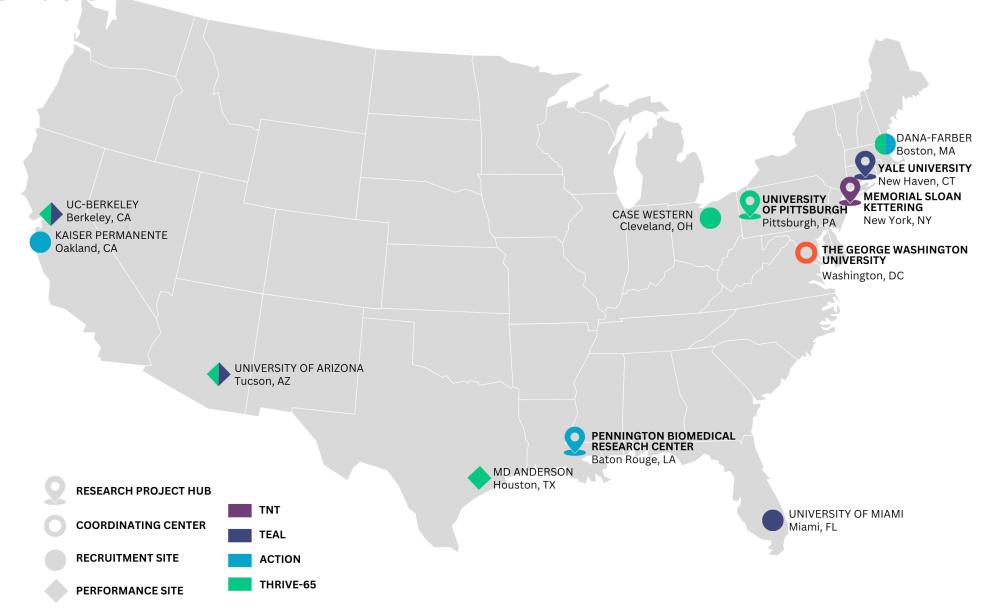
- Women newly diagnosed with breast cancer are interested in participating in a nutrition and exercise intervention during chemotherapy (57% women screened for the trial enrolled in the study).
- The LEANer intervention led to favorable changes in diet quality and physical activity.
- Nutrition Impact Symptoms are common.
- Women completed chemotherapy at higher rates than reported in observational studies, perhaps because of other supportive therapies and/or participating in a trial, leaving little room for improvement in chemotherapy completion (ceiling effect).
- Most common reasons for dose reductions and/or delays were neuropathy (50%), infections (25%) and hematologic toxicities (25%).
- 53% of women randomized to intervention had a pathologic complete response vs. 28% of women randomized to usual care (p = .037)
- Qualitative interviews with women randomized to intervention revealed numerous benefits of the intervention on quality of life.
- Additional analyses will examine the intervention vs. usual care on endocrine therapy adherence, patient-reported outcomes, body composition and blood biomarkers.
- There may be greater potential for clinically relevant effects of nutrition and exercise on treatment adherence in other patient populations with lower overall chemotherapy tolerance.

Exercise and <u>N</u>utrition Interventions to <u>I</u>mprove <u>C</u>ancer <u>T</u>reatment-related <u>O</u>utcomes in Cancer Survivors



Funded by the National Cancer Institute (RFA-CA-21-031 and RFA-CA-21-032)

ENICTO Sites







Trial of Exercise And Lifestyle in Women with Ovarian Cancer



Melinda Irwin, PhD, MPH
Professor & Associate Dean of Research
Yale School of Public Health
Deputy Director, Yale Cancer Center







Tracy Crane, PhD, RDN

Associate Professor, Medical Oncology

Miller School of Medicine, University of Miami

Director, Digital Health & Lifestyle Medicine

Sylvester Comprehensive Cancer Center



Yale

Elena Ratner
Leah Ferrucci
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Maura Harrigan
Courtney McGowan
Linda Gottlieb
Michelle Zupa
Fangyong Li
Leah Puklin
Anlan Cao

U of Miami

Matt Schlumbrecht Frank Penedo Grey Freylersythe Julio Rodriguez Anna Gonzalez Melissa Pentecost Paola Rossi LaShae Rolle

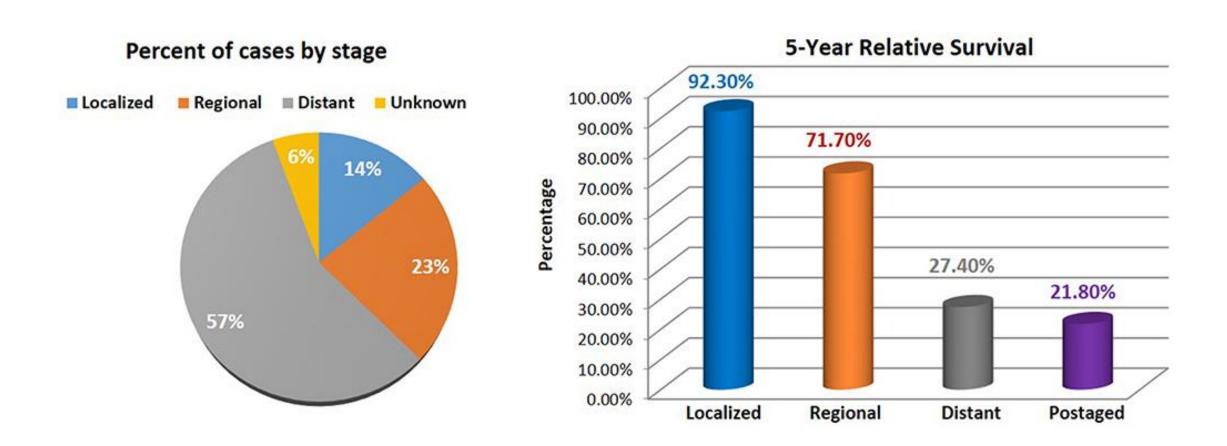
U of Arizona

Cynthia Thomson Jennifer Bea

UC BerkeleyWilliam Evans

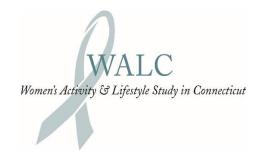
Patient Advocate
Laurel Pracht

Ovarian Cancer



Numerous observational studies report poor adherence to prescribed chemotherapy regimens

Previous Work led us to TEAL

















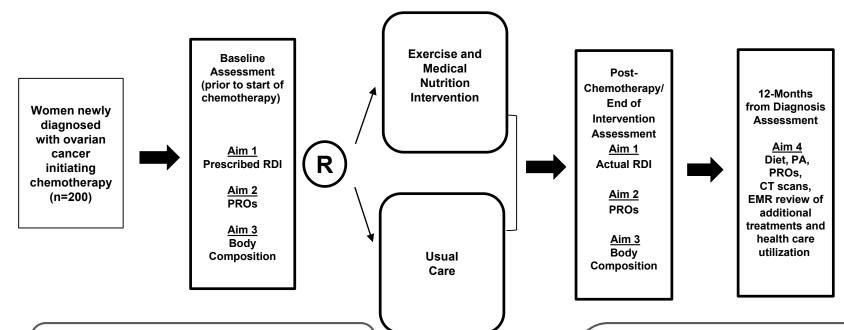
Study Aims



RCT during chemotherapy of a nutrition and exercise intervention versus control in an ethnically diverse sample of 200 women newly diagnosed with ovarian cancer on:

- Aim 1: Adherence to Chemotherapy (RDI, reductions, delays)
- **Aim 2:** Patient-reported outcomes (neuropathy, cognitive function, depression, fatigue, arthralgia, and gastrointestinal disturbances)
- Aim 3: Body composition and muscle mass (CT scans and D3 creatine)
- Also collecting fasting blood to examine effect of intervention on changes in biomarkers

TEAL



Neoadjuvant Chemotherapy:

- 3 cycles chemotherapy prior to surgery
- Surgery
- 3 cycles chemotherapy

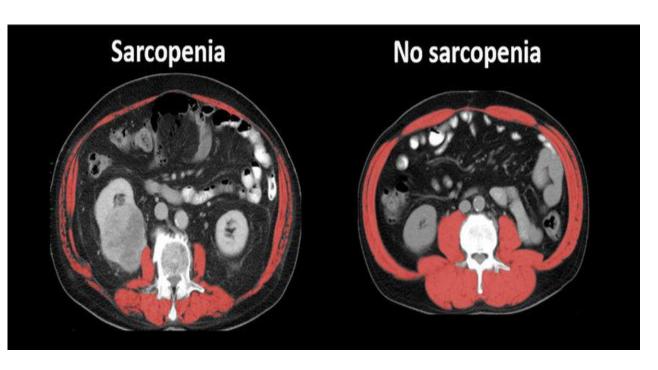
Adjuvant Chemotherapy:

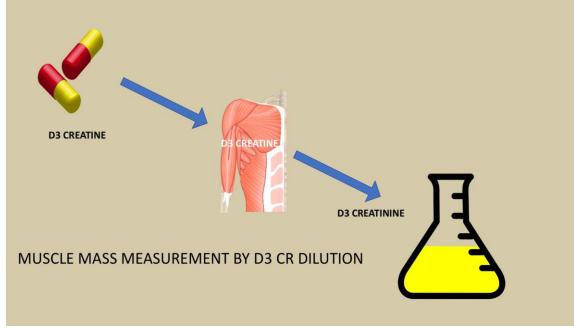
- Surgery
- 6 cycles chemotherapy

Patients with Ovarian Cancer per site:

	<u>Yale</u>	<u>Miami</u>
NHW	85%	30%
Hispanic	4%	60%
Black	8%	10%
Other	3%	<1%

CT Scans and D3 Creatine to Assess Muscle Mass







Evidence-Based Nutrition and Physical Activity Guidelines

Cancer- and Treatment-Specific Recommendations for During Treatment

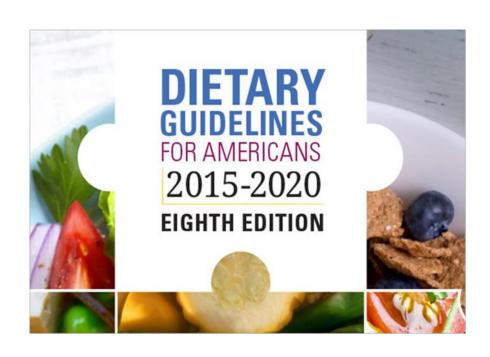




ENICTO Consortium



ASCO and ACSM Guidelines



ACSM and CDC Recommendations



2X per week

Muscle-strengthening activities on 2 or more days a week that work all major muscle groups



Highlights of the ASCO guideline

- Oncology providers should recommend aerobic and resistance exercise during active cancer treatment with curative intent
- 2 Insufficient evidence exists to recommend for or against dietary interventions such as ketogenic or low-carbohydrate diets
- 3 Neutropenic diets are not recommended to prevent infection during active cancer treatment
- Insufficient evidence exists to recommend for or against intentional weight loss or weight gain prevention interventions

Organizations recommending Nutrition and Physical Activity

Table.1 Nutrition care process - expert organization recommendations

Expert society	Malnutri- tion screen- ing	Nutrition assess- ment	Nutrition interven- tion	Exercise	Multimodal intervention	Monitoring	Multidis- ciplinary team
Nutrition							
Academy of Nutrition and Dietetics (AND)	X	X	X			X	X
American Society for Parenteral and Enteral Nutrition (ASPEN)	X	X	X				
European Society for Clinical Nutrition and Metabo- lism (ESPEN)	X	X	X	X	X		
Italian Society of Medical Oncology (AIOM) & Ital- ian Society of Artificial Nutrition and Metabolism (SINPE)	Х	Х	Х			X	Х
Oncology/medicine							
American College of Surgeons (ACS)*	X	X	X				X
American Society of Clinical Oncology (ASCO)	X	X	X				
Association of Community Cancer Centers (ACCC)	X		X			X	X
Clinical Oncology Society of Australia (COSA)	X	X	X	X			X
European Society for Medical Oncology (ESMO)	X		X	X	X	X	
National Comprehensive Cancer Network (NCCN)	X	X	X			X	X
Gastroenterological Society of Taiwan		X	X				
United Kingdom National Multidisciplinary Guidelines	X	X	X	X	X	X	X
Exercise							
American College of Sports Medicine (ACSM)				X			
Exercise for People with Cancer Guideline Develop- ment (Cancer Care Ontario's Program in Evidence- Based Care)				Х			

Why are we not implementing lifestyle interventions in oncology care?

- Clinician-specific challenges:
 - Short duration of clinic visits
 - Inconsistent insurance reimbursement
 - Confusion and mixed messages as to what to recommend
- But landscape is improving:
 - Evidence-based guidelines
 - Resources available
 - Access to specialists
 - NCI funded trials





Interventions Across Cancer Trajectory

What We Know

- PA and better diet quality lower cancer risk and mortality (from observational studies).
- Exercise and diet improve serum biomarkers; more research needed.
- PA improves some treatment side effects; need more evidence (e.g., sarcopenia, cognitive function, neuropathy).
- Awaiting results of lifestyle interventions on disease-free survival.



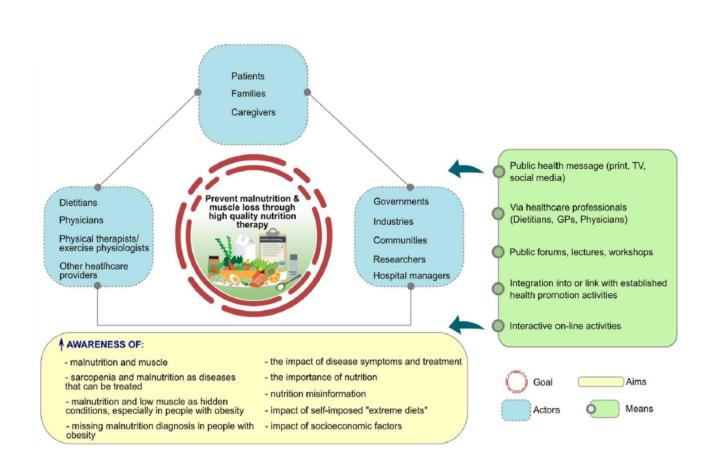
Future Directions

- Interventions on immunotherapy adherence; interventions on tumor response
- Targeted nutrition interventions to prevent and treat malnutrition
- Muscle mass and chemotherapy dosing
- Implement body composition assessments in clinical settings
- Change the standard of care and implement lifestyle behavioral counseling into cancer care

Five Principles to Optimize Clinical Oncology Practice

Expert Panel Recommendations

- 1. Position oncology nutrition at the center of multidisciplinary care
- 2. Partner with colleagues and administrators to integrate a nutrition care process into the cancer care approach
- 3. Screen all patients for malnutrition risk at diagnosis and regularly throughout treatment
- 4. Combine exercise and nutrition interventions before (e.g., prehab), during, and after treatment as oncology standard of care to optimize nutrition status and muscle mass
- 5. Incorporate a patient-centered approach into multidisciplinary care



RCTs with disease recurrence/ mortality end points

	BWEL	CHALLENGE	DIANA 5	GAP 4	LIVES	SUCCESS C
N	3136	962	1241	866	1040	~1400
Disease	Breast	Colon	Breast	Prostate	Ovarian	Breast
Stage	11-111	11-111	1-111	IV	II-IV	11-111
Intervention	2-yr Weight loss	3-yr Ex	4+ yr Med diet + Ex	1-yr Ex	2-yr Diet + Ex	2-yr Weight loss
1º End point	IDFS	DFS	IDFS	OS	PFS	DFS
Correlative	Blood Tissue	Blood	Blood	Blood	Blood	Blood

What patients might want?

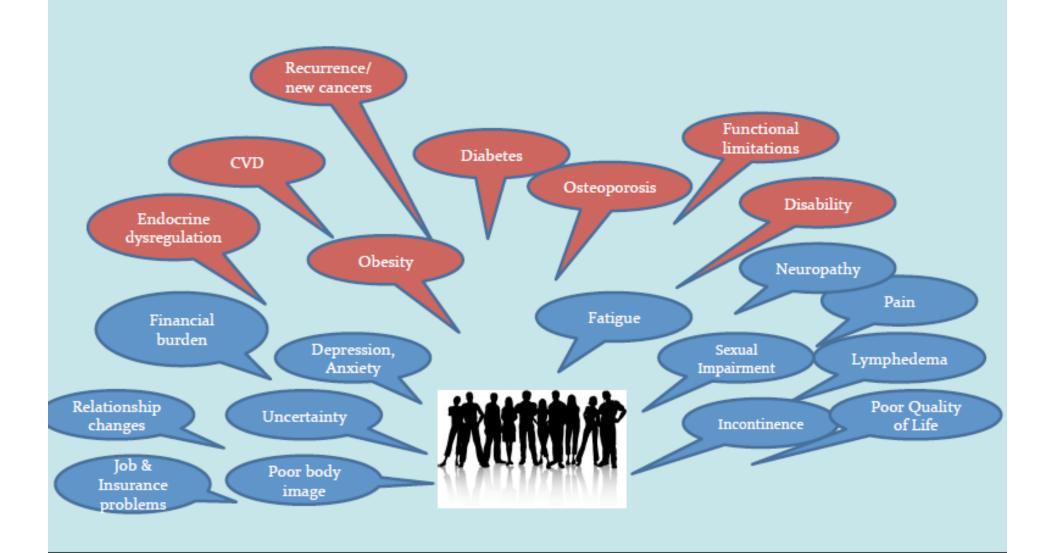




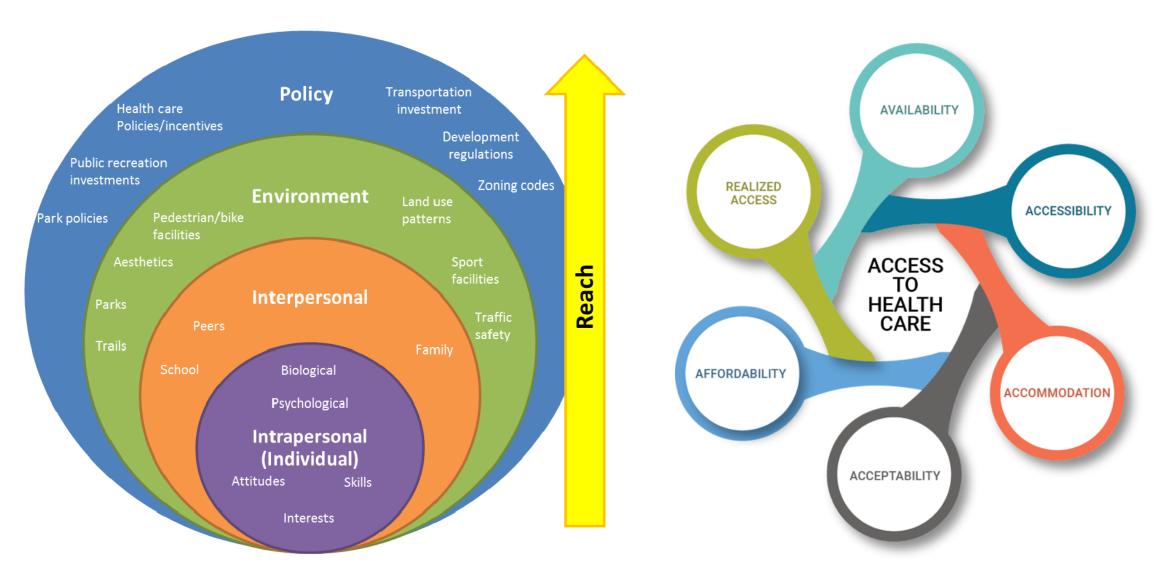


Semaglutide and Tirzepatide

Chronic & Late Effects of Cancer



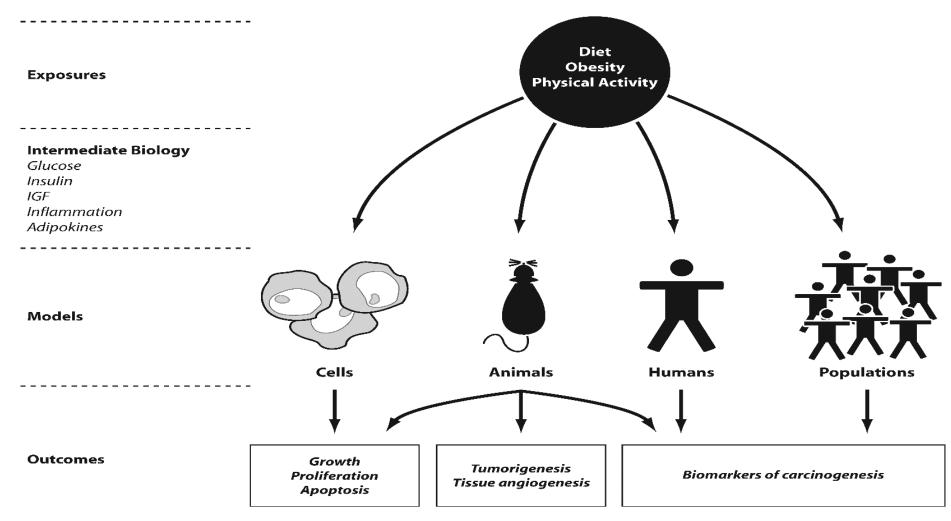
Structural and systems level changes are needed to improve nutrition and physical activity





Transdisciplinary Research on Energetics and Cancer

NCI-R25 funded annual weeklong workshop to train junior faculty and postdocs from around the world on energy balance and cancer http://trectraining.yale.edu









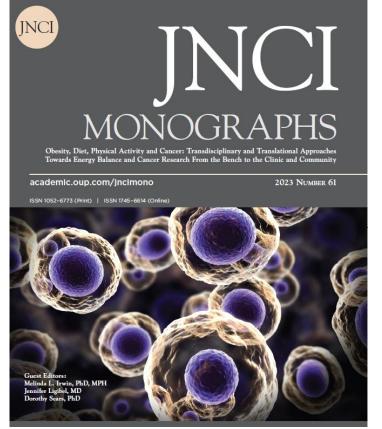








https://ysph.yale.edu/trecrep



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Hosted by: Yale School of Public Health

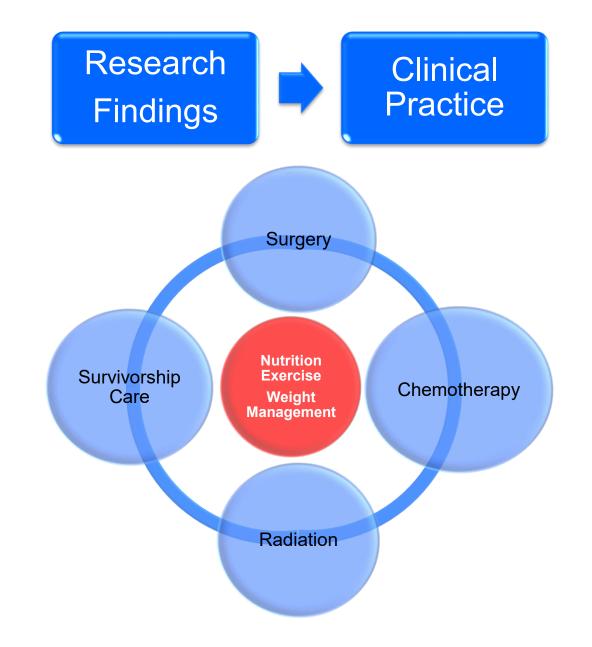
Obesity, Diet, Physical Activity and Cancer: Transdisciplinary and Translational Approaches Towards Energy Balance and Cancer Research From the Bench to the Clinic and Community



This supplement is sponsored by NCI R25CA203650 "Transdisciplinary Research in Energetics and Cancer Training Program (PI: Melinda Irwin)."

Translational and transdisciplinary research in energy balance and cancer: past is prologue Melinda L. Irwin, Dorothy D. Sears, Jennifer Ligibel1	Metabolic and bariatric surgery and obesity pharmacotherapy for cancer prevention: current status and future possibilities Mary C. Playdon, Sheetal Hardikar, Prasoona Karra, Rachel Hoobler, Anna R. Ibele, Katherine L. Cook, Amanika Kumar, Joseph E. Ippolito, Justin C. Brown.
Pharmacokinetics of cancer therapeutics and energy balance: the role of diet intake, energy expenditure, and body composition Sarah A. Purcell, Dieuwertje E. Kok, Tyler Ketterl, Miriam B. Garcia, Lenat Joffe, Justin C. Brown, Christina M. Dieli-Conwright, Grant R. Williams	The impact of surgical weight loss procedures on the risk of metachronous colorectal neoplasia: the differential effect of surgery type, sex, and anatomic location Hisham Hussan, Mohamed R. Ali, Shehnaz K. Hussain, Victoria Lyo, Eric McLaughlin, ChienWei Chiar Henry J. Thompson
The 'omics of obesity in B-cell acute lymphoblastic leukemia Delaney K. Geitgey, Miyoung Lee, Kirsten A. Cottrill, Maya Jaffe, William Pilcher, Swati Bhasin, Jessica Randall, Anthony J. Ross, Michelle Salemi, Marisol Castillo-Castrejon, Matthew B. Kilgore, Ayjha C. Brown, Jeremy M. Boss, Rich Johnston, Anne M. Fitzpatrick, Melissa L. Kemp, Robert English,	Intermittent fasting interventions to leverage metabolic and circadian mechanisms for cancer treatment and supportive care outcomes Faiza Kalam, Dara L. James, Yun Rose Li, Michael F. Coleman, Violet A. Kiesel, Elizabeth M. Cespedes Feliciano, Stephen D. Hursting, Dorothy D. Sears, Amber S. Kleckner
Eric Weaver, Pritha Bagchi, Ryan Walsh, Christopher D. Scharer, Manoj Bhasin, Joshua D. Chandler, Karmella A. Haynes, Elizabeth A. Wellberg, Curtis J. Henry	A review of the impact of energy balance on triple-negative breast cancer Ngozi D. Akingbesote, Dennis Owusu, Ryan Liu, Brenda Cartmel, Leah M. Ferrucci, Michelle Zupa, Maryam B. Lustberg, Tara Sanft, Kim R M. Blenman, Melinda L. Irwin, Rachel J. Perry
Skeletal muscle omics signatures in cancer cachexia: perspectives and opportunities L. Anne Gilmore, Traci L. Parry, Gwendolyn A. Thomas, Andy V. Khamoui	Linking social and built environmental factors to leisure-time physical activity in rural cancer survivors Courtney J. Stevens, Yue Liao, Minxing Chen, Natalia I. Heredia, Hannah Arem, Jasmine Sukumar, Lenat Joffe, Kathryn H. Schmitz, Scherezade K. Mama
Muscle loss during cancer therapy is associated with poor outcomes in advanced ovarian cancer Clarissa Polen-De, Smith Giri, Priyal Fadadu, Amy Weaver, Michaela E. Mcgree, Michael Moynagh, Naoki Takahashi, Aminah Jatoi, Nathan K. Lebrasseur, William Cliby, Grant Williams,	Embedding lifestyle interventions into cancer care: has telehealth narrowed the equity gap? Amy M. Dennett, Kelly A. Hirko, Kathleen J. Porter, Kah Poh Loh, Yue Liao, Lin Yang, Hannah Arem, Jasmine S. Sukumar, Elizabeth A. Salerno
Amanika Kumar	Looking back: a review of policy implications for exercise oncology Mary A. Kennedy, Melanie Potiaumpai, Melissa Maitin-Shepard, Christopher M. Wilson, Anna Campbell, Anna L. Schwartz, Jessica Gorzelitz, Maxime Caru, Chloe Grimmett, Kathryn H. Schmitz
Isabel Pimentel, Joseph E. Ippolito, Ana Elisa Lohmann	Key takeaways for knowledge expansion of early-career scientists conducting Transdisciplinary Research in Energetics and Cancer (TREC): a report from the TREC Training Workshop 2022 Che-Pei Kung, Meghan B. Skiba, Erika J. Crosby, Jessica Gorzelitz, Mary A. Kennedy, Bethany A. Kerr,
opportunities and challenges Urvi A. Shah, Tarah J. Ballinger, Rusha Bhandari, Christina M. Dieli-Cornwright, Kristin A. Guertin, Elizabeth A. Hibler, Faiza Kalam, Ana Elisa Lohmann, Joseph E. Ippolito	Yun Rose Li, Sarah Nash, Melanie Potiaumpai, Amber S. Kleckner, Dara L. James, Michael F. Coleman, Ciaran M. Fairman, Gloria C. Galván, David O. Garcia, Max J. Gordon, Mathilde His, Lyndsey M. Hornbuckle, So-Youn Kim, Tae-Hyung Kim, Amanika Kumar, Mélanie Mahé, Karen K. McDonnell, Jade Moore, Sangphil Oh, Xinghui Sun, Melinda L. Irwin

current status and future possibilities Mary C. Playdon, Sheetal Hardikar, Prasoona Karra, Rachel Hoobler, Anna R. Ibele, Katherine L. Cook, Amanika Kumar, Joseph E. Ippolito, Justin C. Brown
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Key takeaways for knowledge expansion of early-career scientists conducting Transdisciplinary



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Study Participants and Referring Clinicians





