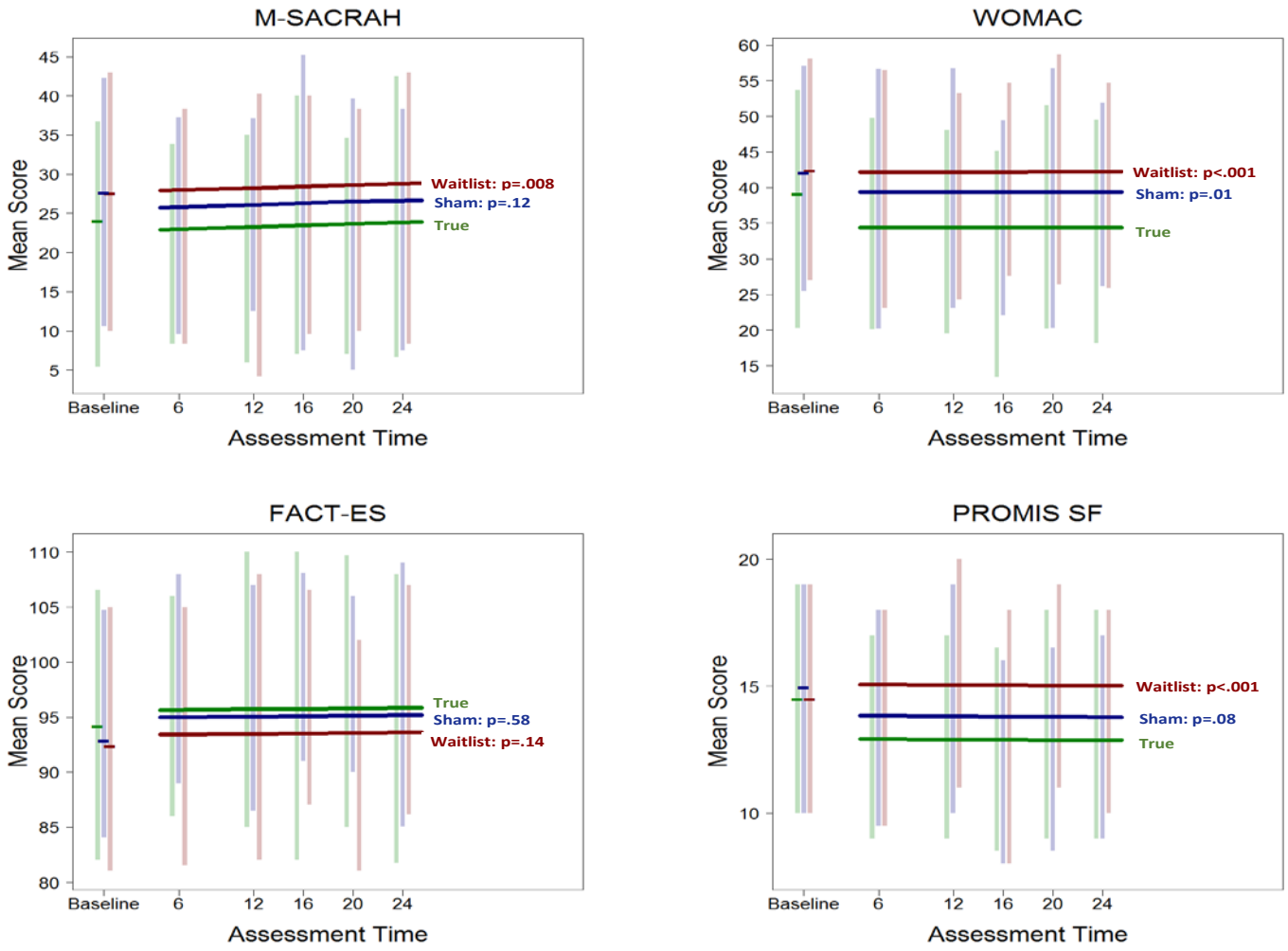
Supplementary Online Content

Hershman DL, Unger JM, Greenlee H, et al. Effect of acupuncture vs sham acupuncture or waitlist control on joint pain related to aromatase inhibitors among women with early-stage breast cancer: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2018.8907

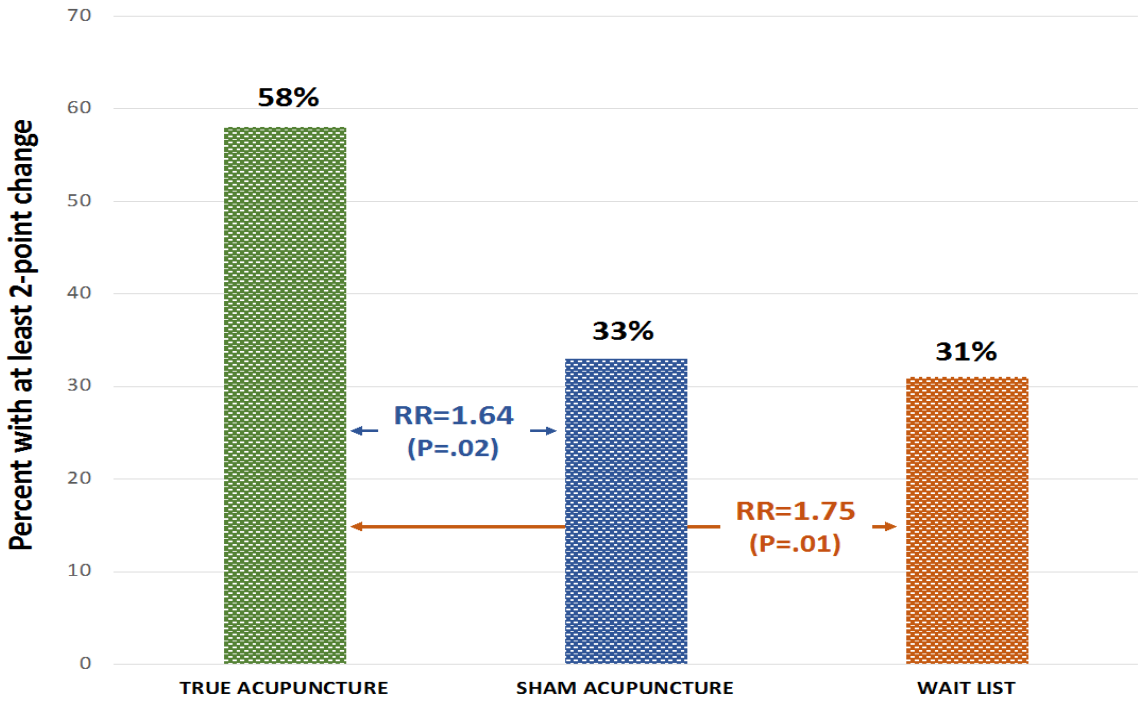
This supplementary material has been provided by the authors to give readers additional information about their work.

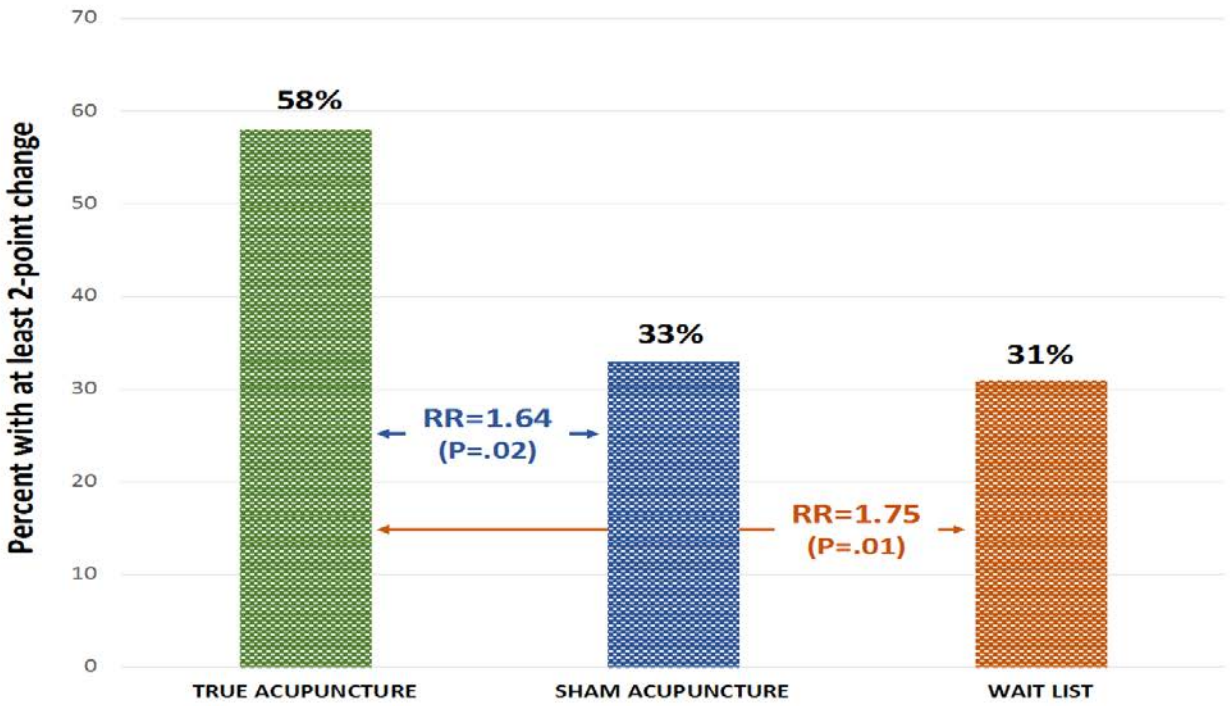
eFigure 1. Linear Mixed-Model Results Through 24 Weeks for the Additional Secondary Endpoints



Linear mixed model results through 24 weeks for the additional secondary endpoints (M-SACRAH, WOMAC, FACT-ES, and PROMIS SF). The vertical boxes indicate the 50% interquartile range for observed true acupuncture scores (green), observed sham acupuncture scores (blue), and observed waitlist control scores (green). The observed mean for each arm at baseline is indicated by the horizontal line within each box. Boxes are offset by a small margin to avoid overlap and clearly show the 50% interquartile range for each arm. The fitted lines for each of the arms are also shown, with the p-value for the comparison of sham acupuncture and, separately, waitlist control, compared to the true acupuncture arm indicated.

eFigure 2. Percent With At Least a 2-Point Change on the Brief Pain Inventory Worst Pain Score





Results for the Brief Pain Inventory – Short Form worst pain score at 6 weeks after randomization. The percent of patients achieving a 2 point improvement (i.e. reduction) in worst pain is shown by arm. The relative risk (RR) between true acupuncture and sham acupuncture (1.64, 95% CI, 1.10-2.44, p=.02) and between true acupuncture and waitlist (RR=1.75, 95% CI, 1.13-2.69, p=.01) are indicated.

eTable 1. Number of Patients With a Given Type and Grade of Adverse Event

	True Acupuncture (n=106) Grade						Sham Acupuncture (n=55) Grade					
ADVERSE EVENTS	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**
Arthralgia	51	40	15	0	0	0	30	16	9	0	0	0
Back pain	104	2	0	0	0	0	55	0	0	0	0	0
Bruising	56	50	0	0	0	0	41	14	0	0	0	0
Dizziness	101	5	0	0	0	0	55	0	0	0	0	0
Ear pain	105	1	0	0	0	0	54	1	0	0	0	0
Edema limbs	103	3	0	0	0	0	55	0	0	0	0	0
Hematoma	105	1	0	0	0	0	55	0	0	0	0	0
Hot flashes	105	0	1	0	0	0	55	0	0	0	0	0
Bleeding at injection site	103	3	0	0	0	0	53	2	0	0	0	0
Intraoperative skin injury	105	1	0	0	0	0	55	0	0	0	0	0
Myalgia	105	1	0	0	0	0	54	1	0	0	0	0
Nausea	106	0	0	0	0	0	54	1	0	0	0	0
Pain	101	5	0	0	0	0	55	0	0	0	0	0
Pain in extremity	105	1	0	0	0	0	55	0	0	0	0	0
Peripheral sensory neuropathy	105	1	0	0	0	0	55	0	0	0	0	0
Presyncope	105	0	1	0	0	0	54	0	1	0	0	0
ROM decreased	101	5	0	0	0	0	53	1	1	0	0	0
Skin/subq tissue ds-Other	105	1	0	0	0	0	55	0	0	0	0	0
MAX. GRADE ANY ADVERSE EVENT	29	61	16	0	0	0	23	22	10	0	0	0

eTable 2. Differences in Proportions With >30% Improvement for Brief Pain Inventory Short Form Scores at Weeks 6 and 12 in Each Group

			Proportion with >30% Improvement[2]				
				Risk Difference (95% CI)		Relative Risk (95% CI)[2]	
Analysis		N	>30% change	True – Sham True – Waitlist	P-value	True/Sham True/Waitlist	P-value
Worst Pain							
Week 6	True	100	49.0%				
	Sham	54	24.1%	24.9% (9.9%-40.0%)	.001	1.95 (1.16-3.28)	.01
	Waitlist	51	23.5%	25.5% (10.3%-40.7%)	.001	2.04 (1.19-3.48)	.009
Week 12	True	101	51.5%				
	Sham	54	46.3%	5.2% (-11.3%-21.7%)	.54	1.09 (0.77-1.54)	.62
	Waitlist	51	15.7%	35.8% (21.9%-49.8%)	<.001	3.24 (1.66-6.34)	<.001
Average Pain							
Week 6	True	100	43.0%				
	Sham	54	25.9%	17.1% (1.9%-32.3%)	.03	1.60 (0.97-2.63)	.07
	Waitlist	51	17.7%	25.4% (11.1%-39.6%)	<.001	2.44 (1.28-4.62)	.006
Week 12	True	101	60.4%				
	Sham	53	45.3%	15.1% (-1.3%-31.6%)	.07	1.31 (0.94-1.83)	.11
	Waitlist	51	29.4%	31.0% (15.3%-46.7%)	<.001	2.04 (1.30-3.21)	.002
Pain Interference							
Week 6	True	100	59.0%				
	Sham	54	44.4%	14.6% (-1.8%-30.9%)	.08	1.36 (0.98-1.89)	.06
	Waitlist	51	35.3%	23.7% (7.4%-40.0%)	.004	1.68 (1.12-2.52)	.01
Week 12	True	101	68.3%				
	Sham	54	64.8%	3.5% (-12.1%-19.1%)	.66	1.06 (0.84-1.33)	.64
	Waitlist	51	37.3%	31.1% (15.0%-47.1%)	<.001	1.85 (1.26-2.70)	.002
Pain Severity							
Week 6	True	100	50.0%				
	Sham	54	33.3%	16.7% (0.7%-32.6%)	.04	1.52 (1.00-2.31)	.05
	Waitlist	51	33.3%	16.7% (0.4%-32.9%)	.04	1.51 (0.98-2.34)	.06
Week 12	True	101	57.4%				
	Sham	54	44.4%	13.0% (-3.4%-29.4%)	.12	1.29 (0.92-1.81)	.15
	Waitlist	51	21.6%	35.9% (21.0%-50.7%)	<.001	2.64 (1.53-4.55)	<.001
Worst Stiffness							
Week 6	True	100	52.0%				
	Sham	54	33.3%	18.7% (2.7%-34.6%)	.02	1.56 (1.03-2.37)	.04
	Waitlist	51	29.4%	22.6% (6.7%-38.5%)	.005	1.76 (1.11-2.78)	.02
Week 12	True	100	50.0%				
	Sham	54	46.3%	3.7% (-12.8%-20.2%)	.66	1.09 (0.78-1.53)	.62
	Waitlist	51	19.6%	30.4% (15.7%-45.1%)	<.001	2.54 (1.42-4.54)	.002

1 – Among patients with follow-up scores

2 – Post-hoc analysis

eTable 3. Observed and Fitted Group Mean Results and Differences in Proportions With ≥30% Improvement for M-SACRAH, WOMAC, FACT-ES, at Weeks 6 and 12 in Each Group

			Group Mean Differences				Proportion with ≥30% Improvement[3]				
			Baseline[1]	Follow-Up	Fitted Difference[2]	P-value[2]		Risk Difference (95% CI)		Relative Risk (95% CI)[2]	
Analysis		N	Mean (95% CI)	Mean (95% CI)	True v Sham True v Waitlist		≥30% change	True - Sham True - Waitlist	P-value	True - Sham True - Waitlist	P-value
M-SACRAH											
Week 6	True	101	33.21 (29.24-37.19	20.66 (17.15-24.17)			60.4%				
	Sham	53	34.49 (29.44-39.55)	27.62 (21.90-33.34)	6.23 (0.92-11.55)	.02	43.4%	17.0% (0.6%-33.4%)	.04	1.38 (0.98-1.95)	.06
	Waitlist	51	30.75 (24.87-36.63)	27.53 (21.83-33.24)	9.40 (4.52-14.28)	≤.001	25.5%	34.9% (19.6%-50.2%)	<.0001	2.34 (1.44-3.83)	≤.001
Week 12	True	102	33.21 (29.24-37.19)	21.38 (17.72-25.04)			57.8%				
	Sham	53	34.49 (29.44-39.55)	25.56 (20.46-30.67)	3.13 (-2.14-8.39)	.25	50.9%	6.9% (-9.6%-23.4%)	.41	1.13 (0.83-1.54)	.43
	Waitlist	51	30.75 (24.87-36.63)	27.07 (21.57-32.57)	8.14 (2.94-13.33)	.003	35.3%	22.6% (6.3%-38.8%)	.007	1.67 (1.13-2.46)	.01
WOMAC											
Week 6	True	101	52.13 (48.75-55.50)	32.35 (28.44-36.25)			60.4%				
	Sham	54	51.38 (46.74-56.03)	40.65 (35.30-46.00)	9.27 (3.73-14.82)	.001	33.3%	27.6% (11.3%-42.8%)	.0008	1.80 (1.19-2.71)	.005
	Waitlist	50	48.81 (44.30-53.32)	41.74 (36.28-47.20)	12.18 (6.76-17.59)	<.001	24.0%	36.4% (21.2%-51.6%)	<.0001	2.51 (1.50-4.21)	≤.001
Week 12	True	102	51.13 (48.75-55.50)	30.55 (26.56-34.54)			60.8%				
	Sham	54	51.38 (46.74-56.03)	35.59 (30.53-40.66)	5.76 (0.15-11.36)	.05	44.4%	16.3% (0.1%-32.6%)	.05	1.37 (0.98-1.91)	.06
	Waitlist	51	48.81 (44.30-53.32)	41.20 (36.06-46.34)	13.19 (7.61-18.77)	<.001	29.4%	31.4% (15.7%-47.1%)	<.0001	2.12 (1.36-3.30)	≤.001
FACT-ES											
Week 6	True	101	87.97 (84.90-21.05)	97.35 (94.13-100.57)			35.6%				
	Sham	54	88.93 (84.73-93.13)	95.01 (91.09-98.92)	-3.38 (-6.92-0.16)	.06	18.9%	16.8% (2.7%-30.9%)	.02	1.89 (1.03-3.48)	.04
	Waitlist	50	90.05 (86.10-94.00)	95.24 (91.27-99.21)	-3.14 (-6.69-0.41)	.08	15.7%	20.0% (6.3%-33.6%)	.004	2.24 (1.14-4.42)	.02
Week 12	True	102	87.97 (84.90-21.05)	98.08 (94.81-101.35)			43.1%				
	Sham	54	88.93 (84.73-93.13)	96.21 (92.20-100.23)	-3.13 (-6.95-0.70)	.11	27.8%	15.4% (0.0%-30.7%)	.05	1.58 (0.98-2.55)	.06
	Waitlist	51	90.05 (86.10-94.00)	93.36 (89.04-97.67)	-5.92 (-9.59 to -2.24)	.002	17.7%	25.5% (11.3%-39.7%)	.0004	2.48 (1.32-4.66)	.005
PROMIS PI-SF											
Week 6	True	101	17.56 (16.62-18.51)	13.20 (12.15-14.25)			57.4%				
	Sham	54	16.48 (15.13-17.84)	14.13 (12.71-15.56)	1.68 (0.16-3.20)	.03	42.6%	14.8% (-1.5%-31.2%)	.08	1.35 (0.96-1.91)	.09
	Waitlist	51	15.86 (14.52-17.19)	13.41 (12.07-14.75)	1.20 (-0.35-2.76)	.13	39.2%	18.2% (1.7%-34.7%)	.03	1.45 (0.98-2.13)	.06
Week 12	True	102	17.56 (16.62-18.51)	12.41 (11.37-13.45)			62.8%				
	Sham	54	16.48 (15.13-17.84)	13.14 (11.81-14.47)	1.51 (0.11-2.91)	.04	51.9%	10.9% (-5.4%-27.2%)	.19	1.18 (0.88-1.60)	.26
	Waitlist	51	15.86 (14.52-17.19)	14.40 (12.82-15.99)	3.18 (1.61-4.76)	≤.001	31.4%	31.4% (15.6%-47.2%)	.0001	1.92 (1.24-2.97)	.003

Abbreviations: FACT-ES=Functional Assessment of Cancer Therapy-Endocrine Subscale; M-SACRAH=Modified Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands; WOMAC= Western Ontario and McMaster Universities Osteoarthritis Index

1 – Among patients with follow-up scores

2 – From multivariable linear regression (for examinations of group mean differences by arm) or Poisson regression (for examination of relative risks), respectively, adjusting for the baseline score and the stratification factor.

3 –Post hoc analysis.

eTable 4. Linear Mixed-Model Results

	Identification of Best Model[1]					Best Model Fit[2]		
	Model type (log-likehood from dummy variable model; p-value) (log-likehood from ordinal categorical model; p-value)					Indicator variable model		Linear time coefficient[3]
	Quadratic interaction	Linear interaction	Quadratic time	Linear time	Best model	True vs. Waitlist	True vs. Sham	
Worst Pain	4169.9; p=.40 4174.4; p=.99	4174.5; p=.78 4175.0; p=1.0	4174.9; p=.75 4174.9; p=.75	4175.0 4175.0	Linear time	1.23 (0.66 to 1.80) p<.001	0.59 (0.34 to 1.14) P=.04	-0.01 (-.03 to 0.01) P=.55
Average Pain	3587.3; p=.85 3588.1; p=.89	3588.5; p=.67 3589.0; p=.67	3589.3; p=1.0 3589.7; p=.75	3589.3 3589.8	Linear time	0.81 (0.33 to 1.29) p=.001	0.56 (0.09 to 1.03) p=.02	-0.01 (-0.02 to 0.004) p=.16
Pain Interference	3586.9; p=.44 3591.5; p=.99	3589.9; p=.41 3591.6; p=.90	3591.7; p=1.0 3591.8; p=1.0	3591.7 3591.8	Linear time	0.76 (0.26 to 1.26) p=.003	0.33 (-0.15 to 0.82) P=.18	-0.01 (-0.03 to 0.006) P=.23
Pain Severity	3511.2; p=.70 3513.1; p=.95	3513.8; p=.82 3514.0; p=.90	3514.0; p=.65 3514.0; p=.65	3514.2 3514.2	Linear time	0.87 (0.40 to 1.33) P<.001	0.41 (-0.04 to 0.87) P=.08	-0.005 (-0.02 to 0.01) P=.48
Worst Stiffness	4156.8; p=.35 4160.2; p=.34	4160.3; p=.35 4161.8; p=.70	4162.4; p=1.0 4162.4; p=.75	4162.4; 4162.5	Linear time	1.27 (0.69 to 1.85) P<.001	0.66 (0.09 to 1.22) P=.02	-0.004 (-0.02 to 0.02) P=.71
M-SACRAH	8018.0; p=.58 8021.6; p=1.0	8020.0; p=.41 8021.6; p=1.0	8021.7; p=.75 8021.8; p=1.0	8021.8 8021.8	Linear time	4.99 (1.33 to 8.66) P=.008	2.86 (-0.70 to 6.42) P=.12	0.05 (-0.06 to 0.16) P=.35
WOMAC	8397.6; p=.84 8398.7; p=.84	8399.7; p=1.0 8400.0; p=1.0	8399.3; p=.53 8399.7; p=.58	8399.7 8400.0	Linear time	7.79 (3.89 to 11.7) P<.001	4.95 (1.15 to 8.76) P=.01	0.002 (-0.13 to 0.14) P=.98
FACT-ES	7326.8; p=.52 7327.5; p=.61	7330.4; p=.74 7330.5; p=.74	7329.6; p=.24 7329.7; p=.24	7331.0 7331.1	Linear time	-2.02 (-4.69 to 0.64) P=.14	-0.74 (-3.32 to 1.85) P=.58	0.007 (-0.07 to 0.09) P=.87
PROMIS PI-SF	5691.8; p=.44 5694.4; p=.43	5693.0; p=.17 5695.5; p=.55	5696.5; p=.75 5696.6; p=.75	5696.6 5696.7	Linear time	2.14 (1.10 to 3.17) P<.001	0.90 (-0.10 to 1.90) P=.08	-0.003 (-0.04 to 0.03) P=.89

1 – Identification of best model was based on testing differences in log likelihood between nested models. The following nested model comparisons were made: quadratic interaction model (with 12 degrees of freedom (df)) compared to simple linear model (with 7 df); linear interaction model (with 9 df) compared to simple linear model (with 7 df); and quadratic time model (with 8 df) compared to linear time model (with 7 df). If the test of the difference in model log likehoods, distributed chi-square with degrees of freedom equal to the difference in degrees of freedom from each model, was <.05, the higher order model (quadratic interaction, linear interaction, quadratic time) was chosen as the best fit. Otherwise, the linear time model was chosen as the best fit model.

2 - Two models were examined, one using separate indicator variables to represent intervention assignment, and one using an ordinal categorical variable to represent intervention assignment.

3 – For each outcome, the linear time coefficient was the same for both the indicator variable model and the ordinal categorical variable model.

eTable 5: Participating Study Sites

Spectrum Health Medical Group, Grand Rapids, MI
Kaiser Permanente Medical Center, Walnut Creek, CA
Columbia University Minority Underserved-NCORP, New York, NY
NCORP of the Carolinas (Greenville Health System), Greenville, SC
St. Luke's Mountain States Tumor Institute (PCRC NCORP), Boise, ID
Fred Hutchinson Cancer Research Center, Seattle, WA
Lahey Hospital & Medical Center – NCORP, Burlington, MA
Good Samaritan Hospital/Oregon Health Science University, Portland OR
Pacific Cancer Research Consortium NCORP, Seattle, Washington
University of Southern California. Los Angeles, CA
University of Utah, Salt Lake City, UT