

# Resistance Exercise in Men Receiving Androgen Deprivation Therapy for Prostate Cancer

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**Purpose:** Androgen deprivation therapy is a common treatment in men with prostate cancer that may cause fatigue, functional decline, increased body fatness, and loss of lean body tissue. These physical changes can negatively affect health-related quality of life. Resistance exercise may help to counter some of these side effects by reducing fatigue, elevating mood, building muscle mass, and reducing body fat.

**Methods:** In a two-site study, 155 men with prostate cancer who were scheduled to receive androgen deprivation therapy for at least 3 months after recruitment were randomly assigned to an intervention group that participated in a resistance exercise program three times per week for 12 weeks (82 men) or to a waiting list control group (73 men). The primary outcomes were fatigue and disease-specific quality of life as assessed by self-reported questionnaires after 12 weeks. Secondary outcomes were muscular fitness and body composition.

**Results:** Men assigned to resistance exercise had less interference from fatigue on activities of daily living ( $P = .002$ ) and higher quality of life ( $P = .001$ ) than men in the control group. Men in the intervention group demonstrated higher levels of upper body ( $P = .009$ ) and lower body ( $P < .001$ ) muscular fitness than men in the control group. The 12-week resistance exercise intervention did not improve body composition as measured by changes in body weight, body mass index, waist circumference, or subcutaneous skinfolds.

**Conclusion:** Resistance exercise reduces fatigue and improves quality of life and muscular fitness in men with prostate cancer receiving androgen deprivation therapy. This form of exercise can be an important component of supportive care for these patients.

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AT PRESENT, in many men with locally advanced or metastatic prostate cancer, androgen deprivation therapy is the major treatment modality.<sup>1,2</sup> Although this treatment has been shown to slow the growth of existing tumors, the associated suppression of testosterone to castrate levels (either medically or surgically) may cause temporary or permanent physical changes such as fatigue, functional decline, increased body fatness, and loss of lean body tissue that can reduce health-related quality of life.<sup>1,3,4</sup> Attenuating the effects of androgen deprivation would be desirable.

Previous observational<sup>5-16</sup> and intervention<sup>17-21</sup> studies involving exercise in patients with cancer have focused primarily on aerobic exercise modalities. These studies indicate that aerobic exercise has beneficial effects on a wide variety of biopsychosocial outcomes (eg, cardiovascular fitness, body composition, self-esteem, mood states, and fatigue) during treatment for a variety of cancers.<sup>22-26</sup> To date, there have been no exercise intervention studies in men with prostate cancer.

Resistance exercise requires the body's musculature to move against some type of resistance.<sup>27</sup> In healthy older men, resistance exercise training elevates mood and helps to build muscle tissue and reduce body fat.<sup>28-36</sup> Little is known about the training adaptation of men with prostate cancer who have castrate levels of testosterone induced by androgen deprivation therapy.

The primary purpose of this study was to determine the effects of resistance exercise on fatigue and health-related quality of life in men with prostate cancer receiving androgen deprivation therapy. Secondary outcomes included muscular fitness and body composition. A priori, we also planned to conduct exploratory analyses on the impact of intent of treatment (curative or

palliative) and length of time treated with deprivation therapy ( $< 1$  year or  $\geq 1$  year) as moderators of the response to exercise.

## METHODS

The trial was coordinated at the Ottawa Regional Cancer Centre (Ottawa, Ontario, Canada). The other participating center was the Cross Cancer Institute in Edmonton (Alberta, Canada). Approval was obtained from the ethics committees at both sites and all patients provided written informed consent.

One hundred and fifty-five men with prostate cancer were recruited between September 1999 and August 2001. They were eligible if they had histologically documented prostate cancer, were scheduled to receive androgen deprivation therapy for at least 3 months after recruitment, and if the treating oncologist provided consent. It was not necessary for patients to be

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newly diagnosed with prostate cancer. Men were excluded if they had severe cardiac disease (New York Heart Association class III or greater), uncontrolled hypertension (blood pressure > 160/95 mmHg), uncontrolled pain, unstable bone lesions, or residence more than 1 hour from the study center.

After preliminary screening by telephone, potential study participants attended a preassessment session. A medical and lifestyle history was taken, prior involvement with physical activity was queried, and fatigue<sup>37</sup> and prostate cancer-specific health-related quality of life<sup>38</sup> questionnaires were completed. Anthropometric measurements (height, weight, waist circumference, and skinfolds) were taken. To determine upper- and lower-body muscular fitness, patients completed a standard load test<sup>39</sup> for chest press and leg press. A blood sample was drawn to determine serum free testosterone and prostate-specific antigen (PSA) levels. Patients were then randomly allocated to treatments.

Randomization, performed using a table of random numbers, was stratified according to center (Ottawa or Edmonton) and intent of treatment (curative or palliative). Patients being treated with curative intent included those receiving androgen deprivation therapy in neoadjuvant and adjuvant settings. Patients being treated with palliative intent included those with metastatic disease. The interventions were resistance exercise (intervention group) or waiting list (control group). The treatment allocation was concealed from the study coordinator until completion of baseline testing and stratification. No blinding of patients was used in treatment group assignment, and they were immediately informed about their group assignment. Blinding was used for data collection. A research assistant with no knowledge of group assignment collected muscular fitness and anthropometric data and scored questionnaire responses.

Men in the intervention group met with a certified fitness consultant within 7 days of the preassessment. The fitness consultant provided patients with the results of their exercise assessment and introduced the personalized resistance exercise program. The participant was led through a standardized series of warm-up and cool-down exercises to be performed at each exercise session. Resistance exercise consisted of a 12-week program of nine strength-training exercises carried out under supervision three times per week, at 60% to 70% of one-repetition maximum (1-RM; the maximum amount of weight that can be lifted once), estimated from the standard load test.<sup>40</sup> Two sets of eight to 12 repetitions of the following nine exercises were performed: leg extension, calf raises, leg curl, chest press, latissimus pulldown, overhead press, triceps extension, biceps curls, and modified curl-ups. Sixty percent of the participant's 1-RM was used as the starting resistance.<sup>40</sup> Patients were instructed to increase the resistance by 5 lb when they were able to complete more than 12 repetitions. Patients were free to complete their program at any time during the fitness centers' hours of operation. No attempt was made to place patients in groups to exercise, although in some cases more than one participant in the intervention group inadvertently showed up to exercise at the same time of day.

Men in the control group were offered the identical exercise advice and guidance; however, it was not provided until after the 12-week waiting period.

Fatigue, health-related quality of life, muscular fitness, and anthropometric measures were repeated 12 weeks after the baseline assessment. The primary outcomes were fatigue and health-related quality of life. Secondary outcomes were muscular fitness and body composition.

The 13-item scale (Functional Assessment of Cancer Therapy-Fatigue) assessed fatigue.<sup>37</sup> The scale includes items relating to the consequences of fatigue as well as symptom expression. The maximum score is 52. The fatigue scale has excellent internal consistency (coefficient alpha = 0.95) and test-retest reliability of 0.90.

Health-related quality of life was measured using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) scale.<sup>38</sup> This instrument includes 27 general questions that provide assessments of physical, social or family, emotional, and functional well-being. It also includes 12 questions that query "additional concerns" specific to prostate cancer and its treatment. The FACT-P has demonstrated construct validity and sensitivity and a test-retest reliability of 0.83.

Muscular fitness was measured using a standard load test.<sup>39</sup> This submaximal test involves the completion of repetitions of two exercises, chest press and leg press, at a defined resistance of 20 kg (chest press) or 40 kg (leg press) at a cadence of 22 repetitions per minute (set by a metronome). The

maximum number of repetitions done before falling behind the required cadence was recorded. The standard load test for chest press is highly correlated ( $r = 0.93$ ) with maximal bench press strength and the test-retest reliability is excellent ( $r = 0.98$ ).<sup>40</sup>

Body composition was assessed indirectly through changes in body weight, body mass index, waist circumference, and subcutaneous skinfolds. The body mass index is calculated as the weight in kilograms divided by the height in meters squared. Skinfold measures were made with standard techniques<sup>41</sup> at four sites (triceps, biceps, subscapular, and iliac crest) according to the method of Durnin and Womersley.<sup>42</sup> Waist circumference was measured at the narrowest part of the torso (above the umbilicus and below the xiphoid process).<sup>43</sup>

The sample size was calculated to detect a difference between groups of 3.0 points on the fatigue scale (SD = 5.0 points). A three-point difference on the fatigue scale is considered to be the minimal clinically important difference.<sup>44</sup> A two-sided test was used with alpha = 0.05% and 80% power. The number of patients required for each treatment was 69.<sup>45</sup> The sample size was also sufficient to detect a difference of 5.0 points on the FACT-P questionnaire (SD = 9.0 points).

All patients randomly assigned to receive treatment were included in the intent-to-treat analysis. We compared the groups at baseline using independent samples  $t$  tests for continuous variables and  $\chi^2$  tests for categorical variables.

For the primary analysis, a  $t$  test was used to compare between-group changes in fatigue (fatigue scale) and disease-specific quality of life (FACT-P) between baseline and 12 weeks. Change over the treatment period was calculated by subtracting the baseline score from the 12-week score. If data were missing because of loss to follow-up, information from the participant's baseline evaluation was used in the analysis, on the basis of the last observation carried forward principle.

Secondary outcomes (muscular fitness and body composition) were analyzed in a manner similar to that used for the primary analysis. Exploratory analyses for planned subgroup comparisons were conducted using length of time treated with deprivation therapy (< 1 year or  $\geq$  1 year), and treatment intent (curative or palliative) as stratification variables. These analyses were conducted for hypothesis-generating purposes.

## RESULTS

### *Intervention and Follow-Up*

A total of 507 eligible patients were approached during the recruitment period, and 155 (30.6%) agreed to participate. Eighty-two men were assigned to the intervention group and 73 men were assigned to the control group. Attendance at the prescribed resistance exercise sessions averaged 79% (28 of 36 sessions). During the intervention period, eight men (9.8%) dropped out in the intervention group compared with 12 men (16.4%) in the control group ( $P = .79$ ). Overall, end-of-treatment (12-week) data were available for 135 of 155 men (87.1%). Between the sites, thirty-nine men in the control group (30.1%) requested the resistance exercise program after their 12-week waiting period. We did not collect further information about the response of these patients to the exercise program.

### *Patient Characteristics*

Characteristics of study patients are listed in Table 1. The groups were balanced in terms of age, body weight, body mass index, time from diagnosis, time receiving hormone therapy, cancer stage grouping, treatment intent, prior physical activity level, and experience with resistance exercise. Types of androgen deprivation therapy are listed in Table 2. The groups were balanced with respect to the proportion of patients receiving monotherapy and combined therapy. (A recent meta-analysis showed patients receiving mono-

**Table 1. Baseline Characteristics of Volunteers Participating in Exercise Study**

Variable	Intervention Group (n = 82)	Control Group (n = 73)	P*
Age, years			
Mean (SD)	68.2 (7.9)	67.7 (7.5)	.66
Weight, kg			
Mean (SD)	88.0 (12.6)	86.7 (13.0)	.53
BMI, kg/m <sup>2</sup>			
Mean (SD)	29.0 (3.5)	28.5 (3.7)	.32
Testosterone, pmol			
Mean (SD)	2.8 (8.8)	5.4 (10.3)	.58
PSA, ng/mL			
Mean (SD)	14.3 (11.0)	9.0 (11.2)	.42
Time since diagnosis, days			
Mean (SD)	980.1 (1,115.4)	762.9 (1,292.6)	.27
Time receiving hormone therapy, days			
Mean (SD)	374.8 (567.8)	402.4 (665.4)	.78
Cancer stage grouping, no. (%)			
Stage I	0 (0.0)	0 (0.0)	.60
Stage II	40 (48.8)	35 (47.9)	
Stage III	11 (13.4)	13 (18.1)	
Stage IV	17 (20.7)	10 (13.9)	
Unassignable group	14 (17.1)	15 (20.8)	
Treatment intent, no. (%)			
Curative	49 (59.8)	46 (63.0)	.74
Palliative	33 (40.2)	27 (37.0)	
Prior activity level, no. (%)			
< 2 times per week	31 (37.8)	26 (35.6)	.95
≥ 3 times per week	51 (62.2)	47 (64.4)	
Prior resistance exercise, no. (%)			
< 2 times per week	64 (78.0)	56 (76.7)	.89
≥ 3 times per week	16 (22.0)	17 (23.3)	

Abbreviations: BMI, body mass index; PSA, prostate-specific antigen.

\*P values for continuous variables are for independent *t* tests comparing baseline values between the intervention group and the control group. P values for categorical variables are for  $\chi^2$  tests. All P values are two-tailed.

therapy had a more favorable quality of life profile than those receiving total androgen blockade.<sup>46)</sup>

#### Effect on Fatigue

At baseline, fatigue scale scores were not different in the two groups ( $P = .24$ ). Changes in fatigue scale scores between baseline and 12-week assessment are shown in Table 3. On the fatigue scale, low scores reflect more interference from fatigue on activities and

roles in daily living. A change score greater than 0 represents a reduction in fatigue, whereas a negative score indicates greater fatigue. In the intervention group, the fatigue scale score increased by 0.8 points, whereas it decreased by 2.2 points in the control group ( $P = .002$  for difference of change scores between groups). Exploratory analyses showed a benefit of resistance exercise for improving symptoms of fatigue regardless of whether men were treated with curative ( $P = .015$ ) or palliative ( $P = .052$ ) intent, or

**Table 2. Types of Androgen Deprivation Therapy**

Type of Treatment	Intervention Group (n = 82)		Control Group (n = 73)		P
	No. of Patients	%	No. of Patients	%	
Monotherapy					.10
LHRH agonist	20	23.7	17	23.1	
Biclutamide	1	1.3	0	0.0	
Flutamide	15	18.4	4	4.6	
Cyproterone acetate	8	9.2	9	12.3	
Combined therapy					.24
LHRH agonist + biclutamide	31	38.2	39	53.8	
LHRH agonist + nilutamide	4	5.3	1	1.5	
LHRH agonist + flutamide	3	3.9	3	4.6	

Abbreviation: LHRH, luteinizing hormone-releasing hormone.

\*P values are for  $\chi^2$  tests comparing types of monotherapy and types of combined therapy between the intervention and control groups. All P values are two-tailed.

**Table 3. Mean Changes and SDs in Fatigue Scale\* Scores Between Groups for All Patients, and Stratified by Treatment Intent or Length of Time Receiving Androgen Deprivation Therapy**

	Pretest		Posttest		Change†		P‡
	Mean	SD	Mean	SD	Mean Change	SD	
All patients							
Intervention (n = 82)	40.8	10.6	41.6	10.5	0.8	5.8	.002
Control (n = 73)	42.5	8.5	40.3	9.4	-2.2	5.8	
Men treated with curative intent							
Intervention (n = 49)	42.9	8.5	43.7	8.8	0.8	5.8	.015
Control (n = 46)	41.6	8.7	39.2	9.7	-2.5	6.9	
Men treated with palliative intent							
Intervention (n = 33)	37.7	12.5	38.4	12.1	0.8	5.9	.052
Control (n = 27)	42.2	8.6	42.2	8.6	-1.8	3.4	
Men receiving ADT for < 1 year							
Intervention (n = 56)	42.6	9.2	43.7	8.7	1.1	6.5	.009
Control (n = 52)	42.2	8.8	39.9	10.1	-2.3	6.5	
Men receiving ADT for ≥ 1 year							
Intervention (n = 26)	36.8	12.2	37.0	12.6	0.2	4.0	.057
Control (n = 21)	43.2	8.1	41.2	7.4	-2.0	3.9	

Abbreviation: ADT, androgen deprivation therapy.

\*Higher scores on the fatigue scale reflect less interference from fatigue on activities and roles in daily life.

†Changes shown occurred over a 12-week intervention period.

‡P values are for independent *t* tests comparing change scores between the intervention group and the control group. All *P* values are two-tailed.

if androgen deprivation therapy had been received for less than 1 year ( $P = .009$ ) or  $\geq 1$  year ( $P = .057$ ).

#### Effect on Health-Related Quality of Life

Baseline scores for the FACT-P were not different between groups ( $P = .27$ ). Changes in FACT-P scores between baseline and 12-week assessment are listed in Table 4. On the FACT-P, low scores reflect lower health-related quality of life and more

concerns specific to prostate cancer and its treatment. A change score greater than 0 represents an improvement in health-related quality of life, whereas a negative score indicates a decline. In the intervention group, the FACT-P score increased by 2.0 points, whereas it decreased by 3.3 points in the control group ( $P = .001$  for difference of change scores between groups). Exploratory analyses showed a benefit of resistance exercise for improving health-related quality of life regardless of whether

**Table 4. Mean Changes and SDs in FACT-P\* Scores Between Groups for All Patients and Stratified by Treatment Intent or Length of Time on Androgen Deprivation Therapy**

	Pretest		Posttest		Change†		P‡
	Mean	SD	Mean	SD	Mean change	SD	
All patients							
Intervention (n = 82)	118.2	16.7	120.2	15.9	2.0	9.1	.001
Control (n = 73)	120.9	13.6	117.6	14.9	-3.3	10.2	
Men treated with curative intent							
Intervention (n = 49)	120.9	15.5	122.6	14.2	1.7	9.5	.015
Control (n = 46)	120.7	13.8	117.3	16.4	-3.4	10.6	
Men treated with palliative intent							
Intervention (n = 33)	114.1	17.9	116.7	17.8	2.6	8.6	.020
Control (n = 27)	121.3	13.6	118.3	12.1	-3.1	9.6	
Men receiving ADT for < 1 year							
Intervention (n = 56)	121.3	15.2	123.0	15.0	1.7	9.5	.014
Control (n = 52)	120.7	12.7	117.8	15.5	-2.9	9.8	
Men receiving ADT for ≥ 1 year							
Intervention (n = 26)	111.5	18.6	114.1	15.8	2.6	8.2	.018
Control (n = 21)	121.5	15.9	117.2	13.6	-4.3	11.2	

Abbreviations: FACT-P, Functional Assessment of Cancer Therapy-Prostate; ADT, androgen deprivation therapy.

\*Higher scores on the FACT-P reflect better health-related quality of life and fewer prostate cancer- or treatment-related concerns.

†Changes shown occurred over a 12-week intervention period.

‡P values are for independent *t* tests comparing change scores between the intervention group and the control group. All *P* values are two-tailed.

men were treated with curative ( $P = .015$ ) or palliative ( $P = .02$ ) intent, or whether androgen deprivation therapy had been received for less than 1 year ( $P = .014$ ) or  $\geq 1$  year ( $P = .018$ ).

#### *Effect on Muscular Fitness*

Baseline scores for chest press (32.0 v 32.3 repetitions;  $P = .92$ ) and leg press (36.4 v 38.4 repetitions;  $P = .68$ ) were not different between the intervention and control groups.

In the intervention group, chest press repetitions increased by 13.1, whereas they decreased by 2.6 in the control group ( $P = .009$  for difference of change scores between groups). Exploratory analyses showed a benefit of resistance exercise for improving upper-body fitness regardless of whether men were treated with curative ( $P < .001$ ) or palliative ( $P = .012$ ) intent, or whether androgen deprivation therapy had been received for less than 1 year ( $P < .001$ ) or  $\geq 1$  year ( $P < .001$ ).

For lower body muscular fitness, leg press repetitions increased by 11.8 in the intervention group and decreased by 1.6 in the control group ( $P < .001$  for difference of change scores between groups). Lower body muscular fitness was enhanced with resistance exercise for men treated with curative ( $P < .001$ ) or palliative intent ( $P = .015$ ). It was also enhanced in men treated with androgen deprivation for less than 1 year ( $P = .002$ ) or  $\geq 1$  year ( $P = .0152$ ).

#### *Effect on Body Composition*

There were no differences between groups for changes in body weight, body mass index, waist circumference, or sum of skinfolds during the intervention period.

#### *Effect on Testosterone and PSA Levels*

At baseline, the groups were balanced for testosterone (2.76 v 5.35 pmol/L in the intervention and control groups, respectively;  $P = .42$ ) and PSA (14.29 v 9.00 ng/mL in the intervention and control groups, respectively;  $P = .39$ ). There were no differences between groups for changes in testosterone or PSA over the intervention period. Testosterone increased by 0.77 pmol/L in the intervention group and by 0.36 pmol/L in the control group ( $P = .24$ ). PSA levels decreased by 1.78 ng/mL in the intervention group and increased by 5.40 ng/mL in the control group ( $P = .31$ ).

## DISCUSSION

This study clearly showed that resistance exercise improved symptoms of fatigue and health-related quality of life in men with prostate cancer receiving androgen deprivation therapy. This is the first study to demonstrate that resistance exercise, rather than aerobic exercise, has a benefit of reducing the symptoms of fatigue related to cancer and its treatment.<sup>20,26,47</sup> A three-point difference on the fatigue scale as observed in this study is similar to the magnitude of improvement observed in people receiving erythropoietin for anemia of cancer.<sup>48</sup> This is also the first study to demonstrate that structured exercise can improve health-related quality of life (including prostate cancer-related concerns) in men with prostate cancer.

It is possible that some of the improvement in fatigue and health-related quality of life seen in the intervention group was

the result of an attention effect. Patients in the intervention group were seen three times per week in a structured environment, whereas patients in the control group were not. We do not believe, however, this was an important cause of the observed benefit of the resistance exercise intervention inasmuch as men in the intervention group were also able to achieve large increases in upper and lower body muscular fitness, averaging 42% and 32%, respectively. These improvements are similar to those observed after resistance exercise training in healthy older men ( $> 60$  years),<sup>29,31</sup> and are a more likely explanation of why fatigue and quality of life were improved.

For the men in this study, muscular fitness improved despite castrate levels of serum testosterone (the mean testosterone level of patients averaged 3.8 pmol/L at baseline). Testosterone levels are related to changes in muscular hypertrophy and gains in muscular fitness. Healthy, young males and females demonstrate an increase in testosterone levels after an acute resistance training session at 80% of 1-RM, and resting testosterone levels are increased in resistance training ( $> 80\%$  of 1-RM) of middle-aged sedentary males.<sup>27</sup> In this study, we maintained training resistance below 70% of 1-RM to reduce the possibility of raising serum testosterone levels. There were no differences between groups for changes in serum testosterone or PSA over the course of the study.

A priori, we considered a number of factors that might affect response to resistance exercise, including intention of treatment (curative or palliative) and length of time treated with androgen deprivation therapy. In our exploratory analyses, we found no evidence of a differential response to resistance exercise in these different circumstances and conclude that the intervention is effective for men being treated with either curative or palliative intent and in men who have received androgen deprivation therapy for short or long periods of time.

We demonstrated that men with prostate cancer were interested in a program of resistance exercise and were able to complete 12-week training program with a high level of adherence and a low dropout rate. Our participation rate was more than 30% of the eligible population, and the men attended more than 75% of their prescribed exercise sessions. These percentages are similar to those we observed in a previous study of aerobic exercise in women with stages I and II breast cancer.<sup>17</sup> In that study, the participation rate was 32.5% of eligible patients and the adherence rate was 71.5% of prescribed exercise sessions. The participation rate in these men with prostate cancer is higher than the 15% to 20% of men with heart disease that participate in cardiac rehabilitation programs.<sup>49-51</sup> We believe several features of the program contributed to the high rate of adherence: the relatively low resistance (60% to 70% of maximum capacity); a safe, secure, supervised exercise environment; features that made exercise more attractive and minimized the response costs (eg, free parking, well-equipped and attractive exercise facilities); and experienced fitness consultants to provide leadership and ongoing positive feedback.

One limitation of this study was our omission of measures of anemia. Anemia is a common feature of advanced prostate cancer<sup>52,53</sup> and is a possible explanation for the differences ob-

served between groups. It would have been helpful to know whether the intervention and control groups were balanced for the presence or absence of anemia at study outset, and the effect of the intervention on hemoglobin levels. Hemoglobin values should be included as a study variable in additional confirmatory studies.

Future studies will need to determine whether there are additional benefits to extending the intervention period beyond 12 weeks (eg, favorable changes in body composition), and the comparative benefits of aerobic versus resistance exercise need to be established. It would be useful to incorporate more sophisticated measures of body composition (eg, deuterium oxide testing, computed tomography scans). This intervention

protocol should be tested in patients with other forms of cancer and other clinical populations suffering from disease-related fatigue.

We conclude that resistance exercise reduces fatigue and improves quality of life and muscular fitness in men with prostate cancer receiving androgen deprivation therapy. This form of exercise can be an important component of supportive care for these patients.

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