Patients’ Preferences for Androgen Deprivation Therapy in the Treatment of Intermediate-Risk Prostate Cancer

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Abstract

Background. For men with intermediate-risk prostate cancer (IRPC), adding short-term androgen deprivation therapy (ADT) to external beam radiation therapy (EBRT) has shown efficacy, but men are often reluctant to accept it because of its impact on quality of life. Methods. We conducted time tradeoffs (score of 1 = perfect health and 0 = death) and probability tradeoffs with patients aged 51 to 78 y who had received EBRT for IRPC within the past 2 y. Of 40 patients, 20 had received 6 mo of ADT and 20 had declined. Utility assessments explored 4 ADT-related side effects: hot flashes, fatigue, loss of libido/erectile dysfunction, and weight gain. Results. The most commonly reported “worst” treatment-related complication of ADT was fatigue (50% in both cohorts) followed by reduced libido/erectile dysfunction (40% in both cohorts). The utilities for fatigue were mean = 0.71 and median = 0.92 and for reduced libido/erectile dysfunction were mean = 0.81 and median = 0.92. Utilities did not differ significantly between cohorts. Assuming a 6-mo course of ADT, men reported being willing to trade 3 mo of life expectancy to avoid fatigue due to ADT and 1.8 mo to avoid sexual side effects. Patients in the ADT cohort were willing to accept the side effects of ADT in exchange for a mean 8% absolute increase in survival, whereas patients in the no ADT cohort required a 16% increase (P < 0.001). Conclusions. When considering treatment with ADT, men with IRPC identified fatigue and sexual dysfunction as the most bothersome side effects. Patients who declined ADT expected a larger survival benefit than those who opted for treatment. Both groups expected a survival benefit exceeding that shown by recent trials, suggesting some men may be selecting treatments inconsistent with their preferences.

Highlights

- This study demonstrates that prostate cancer patients receiving radiation therapy are reluctant to receive androgen deprivation therapy (ADT) most commonly due to anticipated fatigue and loss of libido/erectile dysfunction.
- Men who had received ADT reported they would require an average 8% absolute increase in survival to tolerate its side effects, whereas those who declined ADT would require an average 16% increase.
- Required thresholds are well above the estimated absolute survival benefit for ADT demonstrated in recent clinical trials, suggesting an unmet need for improved patient education regarding the risks and benefits of ADT.

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Intermediate-risk prostate cancer (IRPC) comprises 40% to 50% of all prostate cancers.\(^1,2\) For men electing to receive external beam radiation therapy (EBRT) for the treatment of intermediate-risk prostate cancer, optimal treatment remains controversial. Randomized trials have demonstrated an improvement in disease control with the use of dose-escalated EBRT (75–79 Gray [Gy]) compared with standard dose (66–70 Gy) EBRT.\(^3,5\) Other randomized trials have demonstrated a modest survival advantage from the addition of short-term androgen deprivation therapy (ADT) to standard-dose EBRT compared with standard-dose EBRT alone.\(^6,7\)

An incremental benefit of adding short-term ADT to dose-escalated radiation therapy has been suggested in randomized trials but has not been definitively established in practice.\(^8\) Most recently, interim results from the RTOG 08-15 trial demonstrated no overall survival (OS) benefit with the addition of short-term ADT to dose-escalated EBRT but did show significant improvements in distant metastasis and prostate-cancer specific mortality. A dilemma exists in the uncertain balance between the benefits of adding short-term ADT to dose-escalated radiation therapy and the fatigue, hot flashes, diminished sexual function, and weight gain that may result.\(^9\) This dilemma profoundly complicates the informed choice of treatment by men with intermediate-risk prostate cancer. As such, patient perceptions and preferences may have a large impact on the decision to take or decline ADT.

The impact of short-term ADT on the quality of life and the quality-adjusted life expectancy of these men has not been fully studied. In addition, decision aids have not been developed to guide men who must make treatment decisions that involve tradeoffs of quality of life and length of life. We sought to identify the tradeoffs that men make when deciding whether or not to receive short-term ADT and to model the decision-making process for subgroups to inform decision making that may lead to greater satisfaction and less decisional regret.

**Methods**

**Patient Eligibility and Recruitment**

The Institutional Review Board at a large comprehensive cancer center approved this study (protocol No. PA12-0685). This cohort study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. We reviewed a database of adult men with localized, node-negative, intermediate-risk prostate adenocarcinoma who had undergone dose-escalated EBRT, defined as 75- to 79-Gy total dose, within the last 2 y and selected a convenience sample of patients with ongoing appointments. All patients who had completed EBRT within the preceding 2 y and were returning for routine clinical follow-up visits were asked to participate in the study. Of these, we recruited for participation 20 patients who had received a short-term (6-mo) course of ADT prior to EBRT and 20 patients who had declined a short-term course of ADT. Patients provided written consent to participate in structured utility assessment conducted in English between January 2013 and May 2014. We collected demographic information, including age, self-reported race and ethnicity, marital status, and highest level of education. In-person interviews lasted 45 to 60 min. We provided a $100 gift card to all participants upon completion of the interview.
Decision-Making Preferences for ADT

Participants completed the Degner’s Control Preferences Scale\(^{10,11}\) to assess both the preferred and actual role of each patient in making the decision about ADT. The abbreviated version asked patients to indicate their preferred role in making a final treatment decision, with the following options: 1) I prefer to make the final decision, 2) I prefer to make the final decision with input from my doctor, 3) I prefer that my doctor and I share equally in the decision, 4) I prefer my doctor make the decision with my input, and 5) I prefer my doctor make the final decision for me. We adapted the version for the actual role in making the decision (e.g., “I made the final decision.”). We then collapsed responses to represent active, collaborative, or passive role preferences.

We assessed patient perceptions of physician recommendation for ADT by the question “Did your physician recommend for or against ADT?” Response options included: 1) My physician strongly recommended ADT, 2) My physician recommended ADT but left it up to me, 3) My physician did not recommend for or against ADT, and 4) My physician recommended against ADT.

Preference Assessment

We explored patient preferences using face-to-face interviews with a trained research assistant provided with a script (Supplementary Materials). Patients were initially trained on the time tradeoff (TTO) procedures using blindness in 1 eye and blindness in both eyes as health state benchmarks to ensure they understood the procedures and provided utilities that are ordinally valid (i.e., blindness in both eyes is rated as a poorer health state than blindness in 1 eye). Then, we presented a description of each health state in the current study, one at a time: hot flashes, fatigue, loss of interest in sex and inability to have an erection, and weight gain. We defined hot flashes as: “Sudden feeling of hot sensation inside your body, at times breaking into sweat. They last for several minutes and then they go away. They can occur multiple times per day.” We defined fatigue as: “Feeling tired. Loss of energy or strength. This can occur multiple times per week.” We defined loss of interest in sex as: “Loss of sexual desire and inability to have an erection most of the time. The erections are not as strong or frequent and the climax is poor.” Lastly, we defined weight gain as: “Increase in body weight, usually less than 10 lbs.” Subsequently, we used 3 methods to assess preferences for the health states: ordinal ranking of the “worst” health states, chained TTO method, and probability tradeoff (PTO) method. We first presented the patient with the 4 health states and asked to rank them from worst to best.

For the chained TTO method, we asked the patient a series of iterative questions to determine the period of time in an adverse health state (i.e., a side effect of short-term ADT) that he perceived as equivalent to a period of time in a state of perfect health. We defined a standard time frame of 6 mo for the health state as a starting point. The chained TTO method used 2 stages: respondents were asked to compare a health state against an anchor state followed by return to perfect health in the first stage and then to compare the anchor state with the perfect health state in the second stage. For instance, we offered patients the following 2 options: (option A) 1 y in which you experience loss of libido or (option B) 1 mo in which you have normal libido and are otherwise in perfect health. The patient was tasked with selecting their preferred option, after which we reordered option B after increasing the time period in perfect health until the patient was indifferent between options A and B, after which a utility was calculated. As an example, if a patient was indifferent between 1 y with loss of libido and 10 mo with normal libido and in perfect health, the patient was willing to trade 2 of 12 mo to avoid loss of libido. In that case, the utility value for loss of libido is 10/12, or 0.83 (where a value of 1 is equivalent to perfect health and 0 is equivalent to death).

Llewellyn-Thomas\(^{12}\) first used the PTO method to investigate patients’ required risk reduction in heart disease and stroke related to side effects of medications for hypercholesterolemia and Wilke et al.\(^{13}\) more recently used the method to address the question, “Are the gains in life expectancy associated with long-term ADT for patients with locally advanced prostate cancer treated with EBRT worth the adverse side effects?” Through the present application, we asked a similar question for side effects of short-term ADT. The 2 options used for the PTO assessment are given in Supplementary Table 1. Initially, we presented the 10-y survival mortality estimates (expressed as frequencies in 100 patients) as equal, and the patient was asked to choose an option. As an example, given option B (EBRT plus short-term ADT) with no survival benefit over option A, the rational choice is option A. Subsequently, we reordered the options to the patient after we iteratively reduced (in 1% increments) the survival rate of the chosen option until the patient expressed indifference between the 2 options. The difference in survival rates between the options represents the absolute increase in benefit that short-term ADT must offer for the patient to see the 2 options as equivalent.

Statistical Analysis
Descriptive statistics were computed and comparisons were made using the Mann-Whitney U and Fisher exact tests for continuous and categorical variables, respectively. Statistical analysis was performed using SPSS v27 (Armonk, NY, USA).

Results

Baseline participant characteristics are shown in Table 1. Most patients in both treatment cohorts were White, married or living with a romantic partner, and college graduates. Based on these demographic data, no significant differences between treatment cohorts were identified.

Patient decision-making preferences are displayed in Table 2. The most common preferred role in decision making in both the ADT and no ADT treatment cohorts was “I prefer to make the final decision with input from my doctor.” Of note, a nominally larger proportion of patients (n = 4; 20%) in the cohort that received ADT selected “I prefer my doctor make the final decision with my input.” In addition, a nominally larger proportion of patients (n = 3; 15%) in the cohort that did not receive ADT selected “I prefer to make the final decision.” However, there was insufficient evidence to reject the presupposition that the selected statements were different between groups (P = 0.081). When asked to reflect upon their physicians’ recommendations about ADT, most patients in the ADT-treated cohort selected “my doctor strongly recommended ADT,” whereas the majority in the cohort that did not receive ADT reported “my doctor did not recommend for or against ADT” or “my doctor recommended against ADT.” A significant difference between physician recommendations was observed between the treatment cohorts (P < 0.001).

Regarding the ordinal ranking of health states, in each cohort, 50% of patients selected fatigue to be the worst treatment-related complication, 40% selected loss of interest in sex and inability to have an erection, and 10% selected hot flashes; no significant difference in the worst health state was observed between treatment cohorts (P = 1.000). The most commonly selected “least worst” (best) treatment-related complication was hot flashes among patients who received ADT (55%) and weight gain among those who did not received ADT (60%); a significant difference was observed between treatment cohorts for the “least worst” health state (P = 0.025). A summary of these results is provided in Table 3.

The results of the TTO method are shown in Table 4. On average, patients reported being indifferent between living 3.7 mo in perfect health or 6 mo with the side effect ranked as worst. In addition, patients reported being indifferent between living 1.1 mo with the worst side effect or 6 mo with the “least worst” side effect. On average, men reported being willing to trade 3.0 mo of life expectancy to avoid fatigue, 1.8 mo to avoid sexual side effects due to ADT, and 0.6 mo to avoid hot flashes. For all comparisons, there was no significant difference

Table 1 Patient Sample Characteristics

|                        | Patients who received ADT (n = 20) | Patients who did not receive ADT (n = 20) | P-value |
|------------------------|-----------------------------------|-------------------------------------------|---------|
| Age (mean [SD])        | 67.1 (5.8)                        | 65.3 (6.8)                                 | 0.44    |
| Race/ethnicity         |                                   |                                           |         |
| Asian                  | 0                                 | 2 (10%)                                   | 0.35    |
| Black or African American | 0                               | 1 (5%)                                    |         |
| Hispanic               | 3 (15%)                           | 1 (5%)                                    |         |
| White                  | 17 (85%)                          | 16 (80%)                                   |         |
| Marital status         |                                   |                                           |         |
| Married or living with a romantic partner | 15 (75%)                         | 15 (75%)                                   | 1.00    |
| Single                 | 1 (5%)                            | 0                                         |         |
| Widower                | 0                                 | 1 (5%)                                    |         |
| Divorced               | 4 (20%)                           | 4 (20%)                                    |         |
| Education              |                                   |                                           |         |
| Not a high school graduate | 1 (5%)                           | 0                                         | 0.61    |
| High school graduate   | 1 (5%)                            | 0                                         |         |
| Some college           | 1 (5%)                            | 2 (10%)                                   |         |
| College graduate       | 9 (45%)                           | 12 (60%)                                   |         |
| Post-graduate degree   | 8 (40%)                           | 6 (30%)                                    |         |

aA Wilcoxon rank-sum test was used to compare continuous variables, and a Fisher exact test was used to compare categorical variables.
Summary statistics for calculated utilities are shown in Table 5. Among both treatment cohorts, the side effect with the lowest utility was fatigue (mean 0.69 and median 0.93 for patients receiving ADT; mean 0.74 and median 0.92 for those not receiving ADT), followed by loss of interest in sex and inability to have an erection (mean 0.82 and median 0.88 for patients receiving ADT; mean 0.81 and median 0.92 for patients not receiving ADT). No significant differences were seen between calculated utilities for each of the 4 health states across treatment groups.

The results of the PTO method are shown in Table 6. Patients in the cohort who had received ADT on average reported being willing to accept ADT if there were an expected absolute increase of 8% in survival, whereas patients in the cohort who had not received ADT...
Table 4  Time Tradeoff Method Results

|                         | Patients Who Received ADT (n = 20) | Patients Who Did Not Receive ADT (n = 20) | Difference (95% CI) | P Value |
|-------------------------|------------------------------------|-------------------------------------------|---------------------|---------|
| Perfect health v. worst health state: “At how many months of perfect health would you be indifferent when compared with living 6 mo with the side effect you selected as the worst?” | 5 [1–6] | 4 [1.5–5.5] | +0.1 (−1.3 to +1.5) | 0.847 |
| Median [IQR], mo        | 3.8 [2.4]                          | 3.7 [2.1]                                 |                     |         |
| Worst health state v. second worst health state: “At how many months of the side effect you selected as the ‘worst’ would be indifferent when compared to living 6 mo with the side effect you selected as the second worst?” | 2 [1–3] | 2 [1–3] | −0.3 (−1.2 to +0.6) | 0.857 |
| Median [IQR], mo        | 2.1 [1.3]                          | 2.4 [1.5]                                 |                     |         |
| Worst health state v. third worst health state: “At how many months of the side effect you selected as the ‘worst’ would be indifferent when compared to living 6 mo with the side effect you selected as the third worst?” | 1 [0–3] | 1 [0–2] | +0.6 (−0.3 to +1.5) | 0.273 |
| Median [IQR], mo        | 1.7 [1.6]                          | 1.1 [1.2]                                 |                     |         |
| Worst health state v. least worst health state: “At how many months of the side effect you selected as the ‘worst’ would be indifferent when compared to living 6 mo with the side effect you selected as the least worst?” | 0 [0–2] | 1 [0–2] | −0.3 (−1.3 to +0.8) | 0.383 |
| Median [IQR], mo        | 1.1 [1.6]                          | 1.3 [1.6]                                 |                     |         |

Table 5  Calculated Utilities Associated with Each Health State, Stratified by Treatment Cohorta

|                         | Patients Who Received ADT (n = 20) | Patients Who Did Not Receive ADT (n = 20) | Difference (95% CI) | P Value |
|-------------------------|------------------------------------|-------------------------------------------|---------------------|---------|
| Hot flashes             | 1 [0.93–1.00]                      | 0.95 [0.89–1.00]                          | 0.00 (−0.07 to +0.08) | 0.260 |
| Median [IQR]            | 0.93 [0.14]                        | 0.93 [0.09]                               |                     |         |
| Mean [SD]               |                                    |                                          |                     |         |
| Fatigue                 | 0.93 [0.17–1.00]                   | 0.92 [0.50–0.97]                          | −0.05 (−0.28 to +0.18) | 0.869 |
| Median [IQR]            | 0.69 [0.41]                        | 0.74 [0.31]                               |                     |         |
| Mean [SD]               |                                    |                                          |                     |         |
| Loss of interest in sex and inability to have an erection | 0.88 [0.70–1.00] | 0.92 [0.85–1.00] | +0.01 (−0.15 to +0.18) | 0.978 |
| Median [IQR]            | 0.82 [0.22]                        | 0.81 [0.29]                               |                     |         |
| Mean [SD]               |                                    |                                          |                     |         |
| Weight gain             | 0.97 [0.74–1.00]                   | 1.00 [0.95–1.00]                          | −0.10 (−0.20 to +0.01) | 0.230 |
| Median [IQR]            | 0.86 [0.21]                        | 0.95 [0.10]                               |                     |         |
| Mean [SD]               |                                    |                                          |                     |         |

aA value of 1 is equivalent to perfect health and 0 is equivalent to death.
preferred an average absolute benefit of 16% \((P < 0.001)\). Notably, whereas 60% of patients receiving ADT were willing to accept treatment with a survival absolute increase of \(<5\%\), no patients in the cohort who did not receive ADT would accept treatment under this circumstance.

**Discussion**

In the setting of limited but developing evidence supporting the use of ADT for IRPC, patient perceptions regarding sequelae may have a significant role in determining whether a patient decides to accept ADT. In this study, we found that fatigue and loss of libido/erectile function were the side effects of ADT perceived to have the most significant negative quality-of-life impact for patients receiving EBRT for IRPC. In addition, we demonstrated that patients who received and declined ADT were willing to accept treatment in anticipation of 10-y OS benefits of 8% and 16%, respectively, which exceed the estimates of the OS benefit of ADT reported in recent secondary analyses of large trials. Although utilities for side effects were similar between the 2 groups, the threshold life expectancy increase needed to accept these side effects was higher among the group that declined ADT, suggesting that these patients expected greater frequency or intensity of these side effects.

The potential benefit of ADT in patients receiving dose-escalated EBRT is an evolving area of investigation. A recent secondary analysis of the Prostate Cancer Study (PCS) III showed that patients with unfavorable intermediate-risk disease had no difference in OS with the addition of short-term ADT (10-y rate 75% v. 74%; \(P = 0.60\)).\(^{14}\) Similarly, a secondary analysis of the EORTC 22991 demonstrated that patients with unfavorable intermediate-risk disease treated with short-term ADT had no difference in 10-y OS (80% v. 74.3%; \(P = 0.082\)).\(^{8}\) The ongoing RTOG 08-15 trial reported interim results demonstrating no OS benefit with the addition of short-term ADT to dose-escalated RT (5-y OS 91% v. 90%; \(P = 0.22\)). While final trial results are needed, these data collectively suggest that the primary OS benefit to short-term ADT added to dose-escalated ADT is likely small, even at 10 y following diagnosis.\(^{15}\)

The estimated nominal 10-y OS benefit from these trials was 1.0% in PCS III and 5.7% in EORTC 22991, both of which fall short of the 10-y OS benefits of 8% and 16% needed to be indifferent to taking ADT determined in the current study. This discordance between expectations and trial data suggests that some men may be pursuing treatments that do not align with their underlying preferences. While validation of these findings is needed, there likely exists opportunity for better patient education regarding the risks and benefits of treatment through the informed decision-making process, so that men can make treatment decisions concordant with their underlying preference valuations.

The health state associated with the lowest utility in the current study was fatigue. Fatigue has been reported as among the worst side effects of ADT among patients receiving it for the treatment of prostate cancer. Unlike hot flashes, sexual side effects, or loss of muscle mass, fatigue generally cannot be managed with medications.\(^{16}\) Its prevalence among patients receiving ADT is estimated to be 42% to 68% and is likely compounded by the receipt of EBRT.\(^{17,18}\) In the current study, patients reported being willing to trade 3 mo of life expectancy to be able to avoid ADT-related fatigue entirely, underscoring its profound perceived impact on quality of life, both among patients who had accepted and declined it. Lifestyle changes, including physical exercise and dietary modification, are considered to be the best interventions to mitigate ADT-related fatigue.\(^{19,20}\) In future studies, it will be important to understand if the availability of high-quality data supporting these lifestyle interventions influences how IRPC patients perceive the distress that

| Patients Who Received ADT \((n = 20)\) | Patients Who Did Not Receive ADT \((n = 20)\) | \(P\) Value |
|----------------------------------------|------------------------------------------|-------------|
| Median [IQR] increase in survival      | 5% [3–13%]                               | 15% [13–19%] | <0.001 |
| Mean [SD] increase in survival         | 8% [7%]                                  | 16% (5%)    | <0.001 |
| <5% absolute increase in survival      | 12 (60%)                                 | 0 (0%)      |         |
| 6–10% absolute increase in survival    | 3 (15%)                                  | 4 (20%)     |         |
| 11–15% absolute increase in survival   | 2 (10%)                                  | 10 (50%)    |         |
| 16–20% absolute increase in survival   | 3 (15%)                                  | 2 (10%)     |         |
| >25% absolute increase in survival     | 0 (0%)                                   | 4 (20%)     |         |
fatigue may cause during the course of treatment with ADT.

Several studies have assessed patient decision-making tradeoffs in localized prostate cancer and may provide valuable context. The COMPARE study used a discrete choice experiment tool to understand the preferences of patients with low- and intermediate-risk prostate cancer and found that patients were willing to trade a 7% absolute decrease in survival to have active surveillance over definitive treatment. They were also willing to trade 0.8%, 0.5%, and 0.2% absolute decreases in survival for a 1-mo reduction in time to return to normal activities and 1% absolute improvements in urinary and sexual function, respectively.21 Another study used the TTO and standard gamble utilities to show that men were willing to give up only 10% of remaining life expectancy to achieve perfect urinary and/or sexual function after radical prostatectomy.22 Wilke et al.13 used the PTO method to determine if the gains in life expectancy with long-term ADT for patients with locally advanced prostate cancer treated with EBRT were worth the adverse side effects to patients. The study authors found that patients were willing to trade long-term ADT for short-term ADT with a mean minimally required increment in prostate cancer–specific survival of 8%, falling short of the expected gains seen in trials that preceded the study. Although comparison with these data is limited given the different study scope and question, the mean increase in survival of 8% to 16% needed for patients to accept ADT suggests that men indeed see the side effects as having a substantial impact on their quality of life.

Our study has several limitations. The samples of patients and subgroups used in the analyses are small, limiting our ability to make statistically robust conclusions adjusted for confounders. Results may be subject to recall or confirmation bias given that patients were asked to reflect upon decisions made in the preceding 6 mo to 2 y. In addition, the sample of patients interviewed were largely White and highly educated, which may limit the generalizability of these results to the general population of patients with IRPC. There may be additional selection bias, as patients with stronger opinions about their prostate cancer treatment may have elected to participate in this study, also potentially limiting generalizability. There was a significant difference in physician recommendations for ADT use between the 2 cohorts studied; although variation in recommendations may reflect variability in provider treatment preferences and/or shared decision making, this may also reflect selection bias. If patients with higher-risk disease were more often recommended to receive ADT and patients complied perfectly with these recommendations, the defined groups (ADT v. no ADT) may not represent cohorts of patients with distinct preferences, thereby undermining inferences about the association of patient preferences with utilities; however, responses to the Control Preferences Scale suggest that patients felt they had agency in the decision to take ADT, making this potential pitfall unlikely. In addition, although demographic characteristics between the cohorts did not differ significantly, formal matching of the 2 patient cohorts was not performed. The current study uses the PTO method to assess tradeoffs of OS but not tradeoffs of biochemical failure–free survival, distant metastasis–free survival, or prostate cancer–specific mortality; future studies will need to assess how patients perceive the benefits of ADT through these other disease-related endpoints. Interviews with patients were conducted in 2013 and 2014, and the optimal treatment of IRPC has since evolved. However, the decision to pursue ADT remains a dilemma complicated by a lack of clear evidence.

Despite these limitations, the data presented provide insight into the decision for patients with IRPC to take short-term ADT in conjunction with dose-escalated EBRT and thus remain relevant at the time of publication. Future studies will need to assess patient perceptions regarding other prostate cancer–relevant endpoints and to develop decision aids in the face of emerging data and novel hormone therapies with distinct side effect profiles.

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Supplemental Material
Supplementary material for this article is available on the MDM Policy & Practice website at https://journals.sagepub.com/home/mpp.
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