

# Course and Predictors of Cognitive Function in Patients With Prostate Cancer Receiving Androgen-Deprivation Therapy: A Controlled Comparison

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Published online ahead of print at [www.jco.org](http://www.jco.org) on May 11, 2015.

Supported by Grants No. R01-CA132803 and R25-CA090314 from the National Cancer Institute (P.B.J.) and in part by the Biostatistics Core and Molecular Genomics Core at the Moffitt Cancer Center (Grant No. P30-CA076292 from the National Cancer Institute).

Terms in blue are defined in the glossary, found at the end of this article and online at [www.jco.org](http://www.jco.org).

Authors' disclosures of potential conflicts of interest are found in the article online at [www.jco.org](http://www.jco.org). Author contributions are found at the end of this article.

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0732-183X/15/3318w-2021w/\$20.00

DOI: 10.1200/JCO.2014.60.1963

## ABSTRACT

### Purpose

Men receiving androgen-deprivation therapy (ADT) for prostate cancer may be at risk for cognitive impairment; however, evidence is mixed in the existing literature. Our study examined the impact of ADT on impaired cognitive performance and explored potential demographic and genetic predictors of impaired performance.

### Patients and Methods

Patients with prostate cancer were assessed before or within 21 days of starting ADT ( $n = 58$ ) and 6 and 12 months later. Age- and education-matched patients with prostate cancer treated with prostatectomy only ( $n = 84$ ) and men without prostate cancer ( $n = 88$ ) were assessed at similar intervals. Participants provided baseline blood samples for genotyping. Mean-level cognitive performance was compared using mixed models; cognitive impairment was compared using generalized estimating equations.

### Results

ADT recipients demonstrated higher rates of impaired cognitive performance over time relative to all controls ( $P = .01$ ). Groups did not differ at baseline ( $P > .05$ ); however, ADT recipients were more likely to demonstrate impaired performance within 6 and 12 months ( $P$  for both comparisons  $< .05$ ). Baseline age, cognitive reserve, depressive symptoms, fatigue, and hot flash interference did not moderate the impact of ADT on impaired cognitive performance ( $P$  for all comparisons  $\geq .09$ ). In exploratory genetic analyses, *GNB3* single-nucleotide polymorphism rs1047776 was associated with increased rates of impaired performance over time in the ADT group ( $P < .001$ ).

### Conclusion

Men treated with ADT were more likely to demonstrate impaired cognitive performance within 6 months after starting ADT relative to matched controls and to continue to do so within 12 months after starting ADT. If confirmed, findings may have implications for patient education regarding the risks and benefits of ADT.

*J Clin Oncol* 33:2021-2027. © 2015 by American Society of Clinical Oncology

## INTRODUCTION

A growing body of evidence suggests many patients experience cognitive problems as a consequence of cancer treatment.<sup>1</sup> However, important gaps remain in this area. One is the paucity of studies on patients with prostate cancer, the most common cancer in US men.<sup>2</sup> Concern rests primarily with the 44% of patients with prostate cancer who undergo androgen-deprivation therapy (ADT).<sup>3</sup> In addition to producing adverse effects that can interfere with cognitive functioning (eg, fatigue and depressive symptoms),<sup>4,5</sup> ADT may directly affect cognitive functioning, as

suggested by research showing lower testosterone levels are associated with worse cognitive functioning in healthy older men.<sup>6</sup>

The few studies of cognitive functioning among patients with prostate cancer undergoing ADT have yielded mixed results. Although some have found evidence of cognitive problems,<sup>7</sup> others have not.<sup>8,9</sup> A recent meta-analysis of 14 studies concluded that patients with prostate cancer undergoing ADT performed worse than controls in one of seven cognitive domains for which effect sizes could be calculated (ie, visuomotor ability).<sup>10</sup> However, most studies had important methodologic limitations, including use of cross-sectional designs,

absence of comparison groups, short follow-up periods, and/or limited consideration of clinical significance.<sup>10</sup> In addition, there has been little effort to identify moderators of the impact of ADT on cognitive functioning. Research in patients with cancer receiving chemotherapy has indicated that differences in cognitive functioning among patients with similar treatment histories may be partially explained by certain genetic variants<sup>11,12</sup> and extent of cognitive reserve (ie, innate and developed cognitive capacities).<sup>13</sup> Research in other populations has suggested that depressive symptoms, fatigue, and hot flashes may contribute additional risk of cognitive impairment.<sup>14-17</sup>

We sought to advance understanding of the impact of ADT on cognitive functioning by evaluating patients with prostate cancer over a 12-month period after ADT initiation, concurrently evaluating patients with prostate cancer not exposed to ADT and men with no history of cancer of similar age and education level. To address the issue of clinical relevance, analyses were not limited to comparisons of mean-level performance but also focused on the extent to which cognitive performance was impaired based on standard criteria.<sup>18,19</sup> It was hypothesized that ADT recipients would show worsening mean-level cognitive performance and higher rates of impaired cognitive performance over time than control participants. In addition, exploratory analyses examined genetic variants, patient age, cognitive reserve, and symptomatology as moderators of the impact of ADT on cognitive functioning. Specifically, we examined whether genetic inheritance, age, cognitive reserve, depressive symptoms, fatigue, or hot flash interference in combination with ADT would confer a so-called double hit, in which ADT recipients with at-risk alleles, older age, less cognitive reserve, or greater symptomatology would demonstrate the greatest decrements in cognitive functioning.

## PATIENTS AND METHODS

### Participants

Eligibility criteria for all participants were as follows: age  $\geq$  18 years, ability to speak and read English, educational level  $\geq$  sixth grade, no history of stroke, no demonstrated impaired mental status (Short Portable Mental Status Examination score  $<$  3), and no visual, auditory, or psychiatric conditions that would preclude participation. Additional eligibility criteria for patients with prostate cancer receiving ADT were as follows: diagnosed with nonmetastatic or asymptomatic metastatic prostate cancer, scheduled to start or started ADT in past month and to receive it for  $\geq$  6 months, no treatment for other cancers in previous 12 months, no history of brain cancer or cranial irradiation, and no ADT treatment in previous 12 months or antiandrogen in previous 6 months. Additional eligibility criteria for patients with prostate cancer not treated with ADT were as follows: diagnosed with nonmetastatic prostate cancer, no history of other cancers except nonmelanoma skin cancer, undergone prostatectomy but no other prostate cancer treatment, no history of recurrence, and not receiving testosterone supplementation. Additional eligibility criteria for men with no cancer were as follows: no history of cancer except nonmelanoma skin cancer and not receiving testosterone supplementation.

### Procedure

Data were collected between September 2008 and October 2013. Written informed consent was obtained before initiation of study procedures. Participants were paid \$80 at each evaluation. This study was approved by the University of South Florida Institutional Review Board.

Patients were recruited from the Moffitt Cancer Center (patients with prostate cancer receiving and not receiving ADT) and the James A. Haley Veterans' Hospital (patients with prostate cancer not receiving ADT). Control participants without prostate cancer were recruited through use of informa-

tion obtained from Marketing Systems Group (Fort Washington, PA). Patients with prostate cancer not receiving ADT and participants without prostate cancer were recruited to be matched to patients with prostate cancer receiving ADT on age (within 5 years) and educational level ( $\leq$  12, 13 to 16, or  $\geq$  17 years); patients with prostate cancer not receiving ADT were also matched to those with prostate cancer receiving ADT on time since prostate cancer diagnosis (within 6 months). Baseline assessments were completed by patients with prostate cancer receiving ADT before or within 21 days of starting ADT and 6 and 12 months later. Those with prostate cancer not receiving ADT and participants without prostate cancer were assessed at similar time intervals. Appendix Figures A1 to A3 (online only) provide information about participant flow. The larger numbers of patients with prostate cancer not receiving ADT and participants without prostate cancer reflect that, for participants receiving ADT whose control participant not receiving ADT or control participant without prostate cancer withdrew, an additional matched control was recruited.

### Measures

**Demographic and clinical information.** Self-reported demographics and medical comorbidities<sup>20</sup> were assessed at baseline. Time since diagnosis and Gleason scores were assessed via medical record review.

**Cognitive performance.** Neuropsychological testing was conducted by clinical psychology graduate students trained and supervised by experienced clinical psychologists (H.S.L.J., M.B.-J., P.B.J.). Tests with established reliability and validity in older individuals were used (Table 1), including those recommended by the International Cognition and Cancer Task Force (ICCTF).<sup>18</sup> All tests have previously been used in studies with patients with prostate cancer receiving ADT.<sup>10</sup> Estimated full-scale intelligence quotient was assessed at baseline as a measure of cognitive reserve.

**Self-reported measures.** At baseline, all participants completed the Center for Epidemiologic Studies Depression Scale,<sup>29</sup> the Fatigue Symptom Inventory,<sup>30</sup> and the Hot Flash–Related Daily Interference Scale.<sup>31</sup> These measures have been used previously in prostate cancer research.<sup>32-36</sup>

### Single-Nucleotide Polymorphism Selection

Single-nucleotide polymorphisms (SNPs) were selected based on evidence of association with cognitive impairment, depression, fatigue, or circadian rhythm in clinical or nonclinical populations, with preference given to: location in coding regions or known transcription factor binding sites, non-synonymous polymorphisms, and minor allele frequency (MAF) of  $\geq$  .20 in the HapMap population of Utah residents of northern and western European

**Table 1.** Summary of Neuropsychological Test Battery

Domain	Test
Verbal memory	HVLT-R Total Recall <sup>21</sup>
	HVLT-R Delayed Recall <sup>21</sup>
	WMS-III Logical Memory II <sup>22</sup>
Visual memory	BVMT-R Total Recall <sup>23</sup>
	BVMT-R Delayed Recall <sup>23</sup>
Attention	Color Trails 1 <sup>24</sup>
	WMS-III Digit Span <sup>22</sup>
	WMS-III Spatial Span <sup>22</sup>
	SDMT Items Completed <sup>25</sup>
Executive function	Color Trails 2 <sup>24</sup>
	COWA <sup>26</sup>
	TIADL <sup>27</sup>
Cognitive reserve	NART Full-Scale IQ <sup>28</sup>

Abbreviations: BVMT-R, Brief Visuospatial Memory Test–Revised; COWA, Controlled Oral Word Association Test; HVLT-R, Hopkins Verbal Learning Test–Revised; IQ, intelligence quotient; NART, National Adult Reading Test; SDMT, Symbol Digit Modalities Test; TIADL, Timed Instrumental Activities of Daily Living Test; WMS-III, Wechsler Memory Scale–III.

ancestry.<sup>37</sup> A total of 494 SNPs were initially identified and 384 retained after an iterative custom panel design process.

### Genotyping

Genomic DNA was extracted from blood obtained using Gentra Pure-gene tissue kits (Qiagen, Valencia, CA). DNA samples were genotyped using the Illumina GoldenGate assay (Illumina, San Diego, CA) and genotyped using the BeadStudio algorithm by the Moffitt Molecular Genomics Core.

### Statistical Analyses

Analyses were restricted to the 58 patients with prostate cancer receiving ADT, 84 patients with prostate cancer not receiving ADT, and 88 participants without prostate cancer who completed the baseline assessment and at least one follow-up assessment. Those ineligible based on this rule ( $n = 45$ ) did not differ from eligible participants on demographic or clinical variables within any group ( $P$  for all comparisons  $\geq .10$ ). Fisher's exact and  $t$  tests were conducted to identify group differences on demographic and clinical factors. Those significant at  $P < .10$  were included as covariates in all multivariable analyses. To reduce the number of analyses performed and type I error rate, omnibus tests were performed on mean-level and impaired cognitive performance before proceeding to additional analyses.

Mean-level cognitive performance comprised the average of each participant's  $t$  scores (derived using published norms) on all cognitive tests. Changes in scores over time and their interaction with group membership were examined using mixed models with SAS PROC MIXED software (version 9.4; SAS Institute, Cary, NC), allowing for use of all available data at each assessment without imputing missing data.<sup>38</sup>

In accordance with ICCTF guidelines,<sup>18</sup> impaired cognitive performance was defined as scoring  $\geq 1.5$  standard deviations (SDs) below published norms on  $\geq$  two tests or scoring  $\geq 2.0$  SDs below published norms on  $\geq$  one test. In addition, a second, more stringent<sup>39</sup> criterion that is commonly used<sup>40</sup> in the cancer and cognition literature was applied: scoring  $\geq 2.0$  SDs below published norms on  $\geq$  one test. Change in impaired performance over time was evaluated with generalized estimating equation analyses using SAS PROC GENMOD (version 9.4; SAS Institute), which also allowed for use of all available data at each assessment without imputing missing data.<sup>41</sup> Fully adjusted odds ratios (ORs) compared odds of impairment between groups at each assessment. Consistent with previous research on ADT recipients,<sup>9</sup> logistic regression analyses were used to compare rates of impaired cognitive performance between groups on each test at 12 months. Per ICCTF guidelines,<sup>18</sup> the percentage of participants who demonstrated impaired cognitive performance on zero, one, or  $\geq$  two tests was calculated. The number of tests with impaired performance was compared between groups using logistic regression analyses. Because the ICCTF-recommended criterion for cognitive impairment is for overall impairment, logistic regression analyses used the test impairment criterion of scoring  $\geq 2.0$  SDs below norms. A two-sided  $\alpha$  level of 0.05 was set for statistical significance.

Logistic regression analyses using JMP Genomics (SAS Institute) evaluated genetic predictors of change in impaired cognitive performance using additive and dominant models. Impaired cognitive performance at 12 months was regressed on baseline impaired performance, comorbidities, education, group status, genotype, and group-by-genotype interaction. Analyses were restricted to SNPs in Hardy-Weinberg equilibrium, demonstrating a MAF of  $\geq 1\%$  and missing genotype data in  $< 20\%$  in the current sample. A positive false discovery rate was used to control for multiple comparisons; SNPs with  $q < .05$  were considered statistically significant.<sup>42</sup> Because ancestry informative markers were not measured, and few participants self-identified as non-white, genetic analyses were limited to the 214 participants who self-identified as white to reduce extraneous variance resulting from race.

## RESULTS

### Preliminary Analyses

Table 2 lists demographic and clinical characteristics. The group of patients with prostate cancer receiving ADT reported more comor-

bidities and had higher Gleason scores than the group with prostate cancer not receiving ADT and was less likely to be white or better educated than the groups of patients with prostate cancer not receiving ADT and participants without prostate cancer ( $P$  for all comparisons  $\leq .04$ ). Therefore, comorbidities, race, and years of education were included as covariates in subsequent analyses; Gleason scores were not, because ADT treatment is often prescribed for more advanced disease. At the 12-month assessment, 76% of the ADT group was still receiving ADT.

Because neither mean-level cognitive performance nor impaired cognitive performance differed between the group of patients with prostate cancer not receiving ADT and the group of participants without prostate cancer at any assessment ( $P$  for all comparisons  $\geq .41$ ; Appendix Table A1, online only), these groups were combined into a single control group, thus improving statistical power and reducing the number of analyses performed.

### Differences in Cognitive Performance

Change over time in mean-level cognitive performance did not differ between the ADT group and combined control group ( $P = .71$ ). Group differences were observed in change in impaired cognitive performance over time using both criteria for cognitive impairment ( $P$  for both comparisons  $\leq .05$ ; Fig 1). Using the ICCTF-recommended criterion, rates of impaired performance did not differ between groups at baseline (OR, 1.21; 95% CI, 0.66 to 2.22); however, the ADT group was more likely to demonstrate impaired performance than the control group within 6 (OR, 1.71; 95% CI, 1.01 to 2.89) and 12 months (OR, 2.42; 95% CI, 1.27 to 4.61). Similarly, with the more stringent impairment criterion, rates of impaired performance did not differ between groups at baseline (OR, 1.00; 95% CI, 0.53 to 1.89); however, the ADT group was more likely to demonstrate impaired performance than the control group within 6 (OR, 1.72; 95% CI, 1.03 to 2.87) and 12 months (OR, 2.97; 95% CI, 1.54 to 5.72). Using both impairment criteria, impaired performance decreased over time in the 12-month period in the control group ( $P$  for both analyses  $\leq .05$ ) but did not change in the ADT group ( $P$  for both analyses  $\geq .22$ ). This pattern of results remained when the four participants receiving ADT who completed the baseline assessment shortly after ADT initiation and the 13 participants initially receiving ADT but no longer receiving ADT at 12 months were excluded.

Analyses examining the number of impaired tests indicated no group differences at baseline or within 6 months ( $P$  for both comparisons  $\geq .15$ ); however, the ADT group was more likely to be impaired on  $\geq$  two tests within 12 months ( $P = .001$ ; Fig 2). Rates of impaired performance by test are listed in Table 3. The ADT group was more likely to demonstrate impaired performance on Color Trails 2 ( $P = .05$ ).

### Predictors of Change in Impaired Cognitive Performance

Of 384 SNPs measured, 31 were excluded based on the quality-control parameters described. Using the ICCTF-recommended criterion, 15 SNPs were associated with change in impaired cognitive performance using the additive model, and 12 were associated using the dominant model ( $P$  for both comparisons  $< .05$ ; Data Supplement). Using the more stringent criterion, 25 SNPs were associated with change in impaired cognitive performance using the additive model, and 33 were associated using the dominant model ( $P$  for both

**Table 2.** Demographic and Clinical Characteristics of Sample (N = 231)

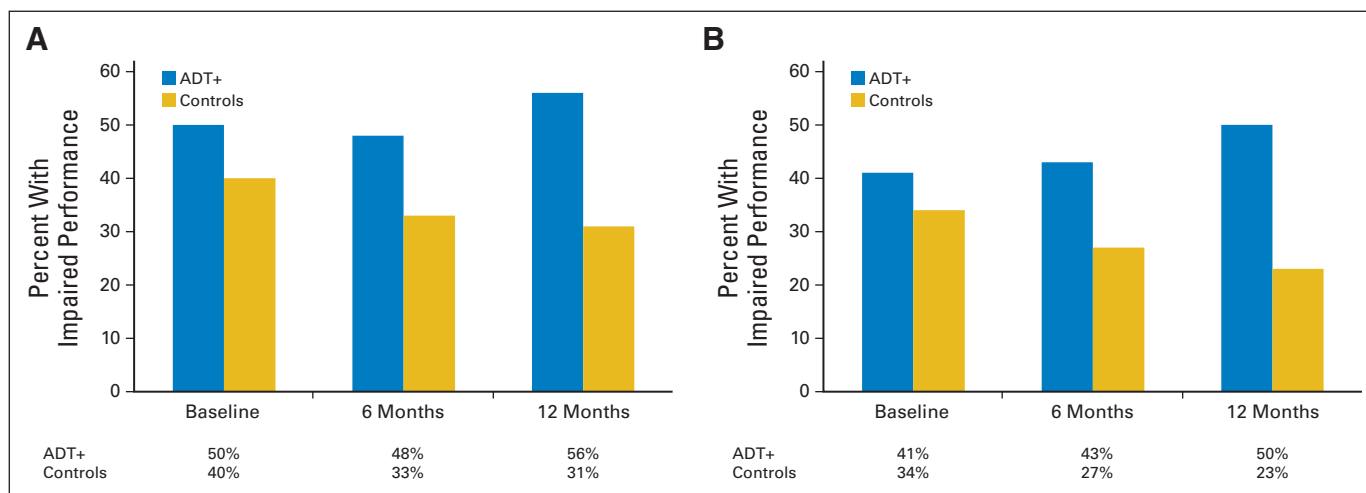
Characteristic	ADT+ (n = 58)		ADT- (n = 84)		CA- (n = 88)		<i>P</i> *		
	No.	%	No.	%	No.	%	ADT+ Versus ADT-	ADT+ Versus CA-	ADT+ Versus All Controls
Age, years									
Mean	67.31		67.72		69.10		.76	.21	.36
SD	8.87		7.37		8.00				
Time since diagnosis, years							.34	—	—
Mean	3.68		4.45		—				
SD	5.03		4.68		—				
Comorbidity index score							.003	.32	.03
Mean	2.90		2.41		2.72				
SD	1.05		0.85		1.09				
Education, years							.03	.03	.01
≤ 12	23	40	17	20	18	21			
13 to 16	29	50	50	60	54	61			
≥ 17	6	10	17	20	16	18			
Race							.02	.04	.004
White	49	84	81	96	84	95			
Nonwhite	9	16	3	4	4	5			
Ethnicity							.65	.65	.38
Hispanic	1	2	3	4	4	5			
Non-Hispanic	57	98	81	96	84	95			
Gleason score							< .001	—	—
4 to 6	9	16	38	45	—	—			
7	22	38	39	46	—	—			
8	18	31	2	2	—	—			
9 to 10	6	10	0	0	—	—			
Missing	3	5	5	6	—	—			

Abbreviations: ADT+, patients with prostate cancer receiving androgen-deprivation therapy; ADT-, patients with prostate cancer not receiving androgen-deprivation therapy; CA-, participants without prostate cancer; SD, standard deviation.

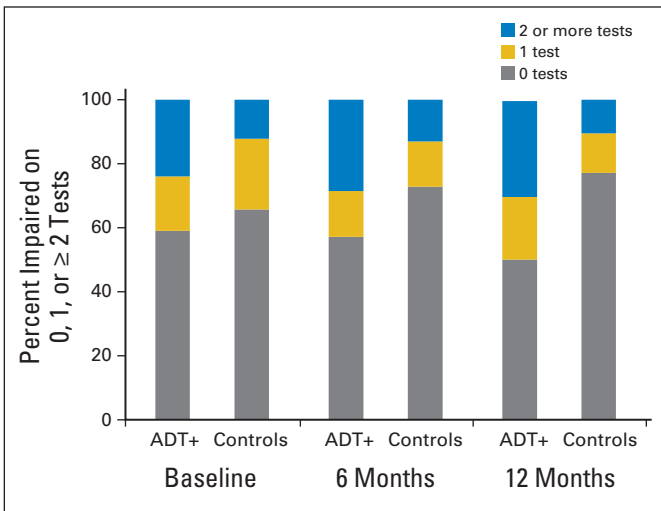
\**P* values calculated using Fisher's exact tests for categorical variables and *t* tests for continuous variables. Missing levels were excluded from calculation of *P* values.

comparisons  $< .05$ ; Data Supplement). One variant (rs1047776 in *GNB3*) also met the cutoff of  $q < .05$  using this criterion. Whereas the rate of impaired cognitive performance decreased over time in the control group and in patients with prostate cancer receiving ADT with

$\geq$  one A allele (AA or AG), it more than doubled over time in the 44% of patients with prostate cancer receiving ADT with wild type (GG; Fig 3). Patients receiving ADT with wild type demonstrated higher odds of impaired cognitive performance within 12 months than patients



**Fig 1.** Observed rates of cognitive impairment in group of patients with prostate cancer receiving androgen-deprivation therapy (ADT+) and control group. Criteria for impaired cognitive performance: (A) scoring  $\geq 1.5$  standard deviations (SDs) below published norms on  $\geq 2$  tests or 2.0 SDs below published norms on  $\geq 1$  test (group differences in change over time  $P = .05$ ); (B) scoring  $\geq 2.0$  SDs below published norms on  $\geq 1$  test (group differences in change over time  $P = .01$ ).



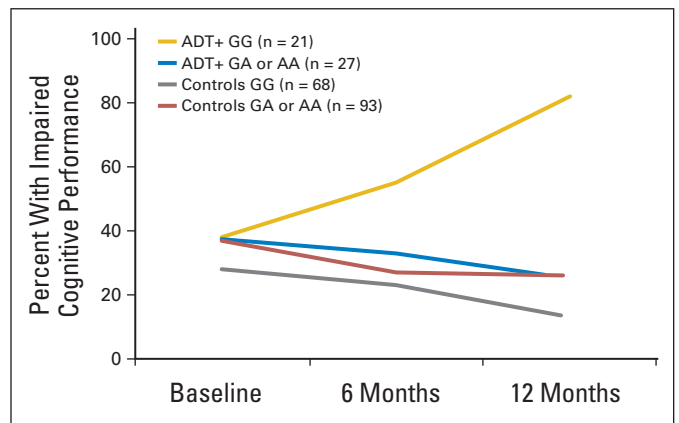
**Fig 2.** No. of tests on which participants demonstrated performance  $\geq 2.0$  standard deviations below published norms at each assessment. ADT+, patients with prostate cancer receiving androgen-deprivation therapy.

receiving ADT with  $\geq$  one A allele (OR, 14.00; 95% CI, 2.97 to 66.09). Logistic regression analyses indicated that age, baseline cognitive reserve, depression, fatigue, and hot flash interference did not moderate the impact of ADT on change in impaired cognitive performance using either impairment criterion ( $P$  for all comparisons  $\geq .09$ ).

**Table 3.** Unadjusted Rates of Impaired Cognitive Performance on Each Test at 12 Months

Cognitive Test	Percentage With Impaired Performance*		P†
	ADT+	Controls	
<b>Verbal memory</b>			
HVLT-R Total Recall	14	5	.33
HVLT-R Delayed Recall	26	11	.10
WMS-III Logical Memory II	4	6	.27
<b>Visual memory</b>			
BVMT-R Total Recall	14	5	.25
BVMT-R Delayed Recall	10	6	.92
<b>Attention</b>			
Color Trails 1	16	5	.08
WMS-III Digit Span	2	1	.85
WMS-III Spatial Span	2	1	.93
SDMT	0	0	—
<b>Executive function</b>			
Color Trails 2	16	4	.05
COWA	14	5	.17
TIADL	2	1	.83

Abbreviations: ADT+, patients with prostate cancer receiving androgen-deprivation therapy; BVMT-R, Brief Visuospatial Memory Test-Revised; COWA, Controlled Oral Word Association Test; HVLT-R, Hopkins Verbal Learning Test-Revised; SDMT, Symbol Digit Modalities Test; TIADL, Timed Instrumental Activities of Daily Living Test; WMS-III, Wechsler Memory Scale-III.  
 \* $\geq 2.0$  standard deviations below norms on  $\geq$  one test.  
 †P values calculated using logistic regression analyses controlling for medical comorbidities, race, and years of education.



**Fig 3.** Observed rates of scoring  $\geq 2.0$  standard deviations below norms on  $\geq$  one test in group of patients with prostate cancer receiving androgen-deprivation therapy (ADT+) and control group by rs1047776 genotype.

**DISCUSSION**

Although there were no differences between groups in changes in mean-level performance, ADT-treated patients were more likely to exhibit impaired cognitive performance than a control group of prostatectomy-treated patients with prostate cancer and men with no history of prostate cancer. This was true using either criterion for impaired cognitive performance. The odds of impaired performance in ADT recipients were approximately 70% higher than in controls within 6 months and  $>$  twice that of controls within 12 months. ADT recipients were also more likely to show impaired performance on multiple tests within 12 months and perform at an impaired level on a test of executive function.

These findings stand in contrast to those from a previous study, in which cognitive functioning was also assessed over a 12-month period in ADT recipients and in prostate cancer and healthy control groups.<sup>9</sup> In that study, the authors found no evidence of higher rates of impaired performance among ADT-treated patients and no differences in rates of impairment on specific tests.<sup>9</sup> Differences in criteria used to define impairment may explain the divergent findings. The previous study defined impairment as a decline of  $\geq$  one SD below baseline level on  $\geq$  one test, whereas in our study, it was defined using two sets of criteria, more in line with existing guidelines,<sup>18</sup> allowing for direct comparison with other studies in the cancer literature.<sup>18,40,43-45</sup> Interestingly, both studies found evidence suggesting that practice effects (ie, improvement over time as function of repeated exposure to same tests) were limited primarily to control groups. These practice effects underscore the importance of including control groups exposed to the same neuropsychological tests and suggest that a key feature of ADT-related cognitive changes may be inability to learn based on prior experience rather than sudden and obvious decline in current ability. Both studies generally failed to find differences in rates of impairment on specific tests within 12 months. In our study, ADT recipients demonstrated impaired performance on one test of executive function but not on two others. Taken together, the findings suggest there is no domain-specific pattern of cognitive impairment associated with ADT. Accordingly, clinicians may find that ADT-treated patients complaining of cognitive change report a variety of problems.

This is the first study to our knowledge to examine whether genetic polymorphisms moderate the impact of ADT on cognitive function. Previous research in patients with cancer has suggested that polymorphisms in certain genes (eg, *APOE* and *COMT*) confer increased risk for cancer-related cognitive changes.<sup>11,12,46,47</sup> Although variants in these genes were included in our study, they were not associated with cognitive function. In contrast, rs1047776 in *GNB3* was found to be associated with cognitive decline among patients but not controls. *GNB3*, involved in modulating transmembrane signaling pathways, was examined based on research suggesting associations with cognitive function and several patient-reported outcomes in noncancer populations.<sup>48,49</sup> Most previous research has focused on rs5443 (C825T), which is in high linkage disequilibrium with rs1047776 ( $D' = .92$ ),<sup>50</sup> reporting that it is associated with cognitive function, sleep, depression, hypertension, and obesity.<sup>51-54</sup> To our knowledge, only one other study has reported on rs1047776, finding that the A ( $\nu$ G) allele was associated with worse sleep in older adults.<sup>53</sup>

Our study has several limitations. It was observational in design and recruited a relatively small sample size. Larger observational studies and randomized trials need to be conducted to more definitively evaluate the impact of ADT on cognitive function. Several patients completed the baseline assessment shortly after ADT initiation, and some were no longer receiving ADT at 12 months. However, excluding these patients did not change the pattern of significant findings. Some cognitive domains assessed in previous studies, such as working memory, were not assessed in our study. No corrections were made for multiple statistical comparisons in the primary analyses; however, an omnibus approach to evaluating cognitive changes was used to conserve the number of comparisons performed. The sample possessed limited racial and ethnic diversity and was composed primarily of college-educated individuals. Controls with history of prostate cancer were limited to patients treated with prostatectomy; whether the same pattern of differences would be evident using a control group of patients treated with radiotherapy instead is unknown. Genetic analyses were limited to those who self-identified as white, because

ancestry-informative markers were not measured, thereby limiting the generalizability of the genetic findings. Future studies should aim to validate and replicate the genetic findings. Lastly, because assessments were only conducted at 6 and 12 months after starting ADT, this study could not determine whether group differences emerged before the 6-month assessment. Nevertheless, this study is among the largest controlled prospective, longitudinal investigations of cognitive functioning in ADT-treated patients with prostate cancer and the first to our knowledge to report on the potential moderating role of genetic polymorphisms on cognitive functioning in this patient population.

In conclusion, these findings serve to raise awareness that some patients with prostate cancer receiving ADT may experience changes in cognitive function within the first 6 months after starting ADT that are likely to persist through 12 months. These findings may have implications for discussions of risks and benefits of ADT. Clinicians may also consider inquiring about changes in cognitive functioning that may have occurred after starting ADT and refer patients for assessment and treatment as needed.

#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at [www.jco.org](http://www.jco.org).

#### AUTHOR CONTRIBUTIONS

**Conception and design:** Brian D. Gonzalez, Heather S.L. Jim, Margaret Booth-Jones, Brent J. Small, Jong Y. Park, Paul B. Jacobsen  
**Provision of study materials or patients:** Philippe E. Spiess, Mayer N. Fishman  
**Collection and assembly of data:** Brian D. Gonzalez, Heather S.L. Jim, Margaret Booth-Jones, Jong Y. Park, Paul B. Jacobsen  
**Data analysis and interpretation:** All authors  
**Manuscript writing:** All authors  
**Final approval of manuscript:** All authors

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## GLOSSARY TERMS

**allele:** an alternative form of a gene (in diploids, one member of a pair) that is located at a specific position on a specific chromosome.

**androgen deprivation therapy (ADT):** treatment that suppresses or blocks the production or action of male hormones.

**genotype:** the specific genetic makeup of a given individual. Although genotypes give rise to the phenotype of an individual,

genotypes and phenotypes are not always correlative. For example, some genotypes are expressed only under specific environmental conditions.

**single nucleotide polymorphism (SNP):** natural variations in the genomic DNA sequence present in greater than 1% of the population, with single nucleotide polymorphisms representing DNA variations in a single nucleotide. Single nucleotide polymorphisms are being widely used to better understand disease processes, thereby paving the way for genetic-based diagnostics and therapeutics.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

### Course and Predictors of Cognitive Function in Patients With Prostate Cancer Receiving Androgen-Deprivation Therapy: A Controlled Comparison

*The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to [www.asco.org/rwc](http://www.asco.org/rwc) or [jco.ascopubs.org/site/ifc](http://jco.ascopubs.org/site/ifc).*

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No relationship to disclose

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No relationship to disclose

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**Consulting or Advisory Role:** Onyx Pharmaceuticals, Philips Healthcare

**Research Funding:** Pfizer, On Q Health

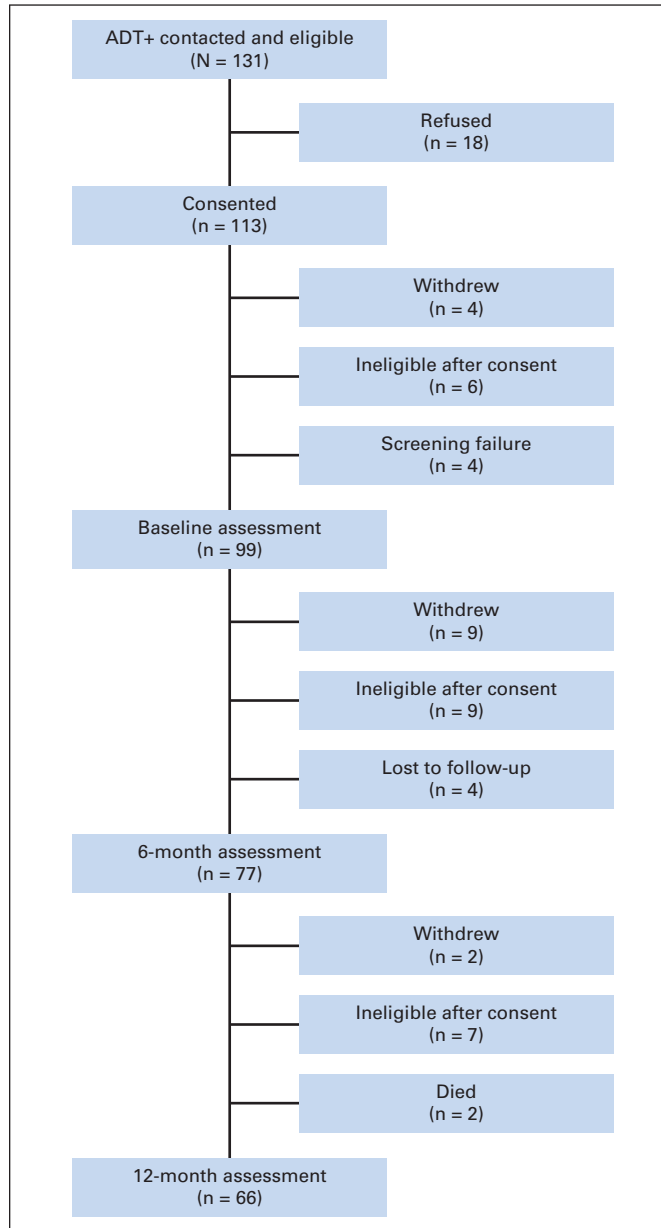
**Travel, Accommodations, Expenses:** Onyx Pharmaceuticals



**Appendix**

<b>Table A1.</b> Summary of Neuropsychological Test Battery		
Group	Impairment Criterion (%)	
	≥ 1.5 SDs on ≥ Two Tests or ≥ 2.0 SDs on ≥ One Test	≥ 2.0 SDs on ≥ One Test
ADT+		
Baseline	50	41
6 months	48	43
12 months	56	50
ADT-		
Baseline	38	31
6 months	37	30
12 months	32	23
CA-		
Baseline	41	37
6 months	28	25
12 months	31	23

Abbreviations: ADT+, patients with prostate cancer receiving androgen-deprivation therapy; ADT-, patients with prostate cancer not receiving androgen-deprivation therapy; CA-, participants without prostate cancer; SD, standard deviation.



**Fig A1.** Participant flow for patients with prostate cancer receiving androgen-deprivation therapy (ADT+).

Cognitive Function in Patients With Prostate Cancer Receiving ADT

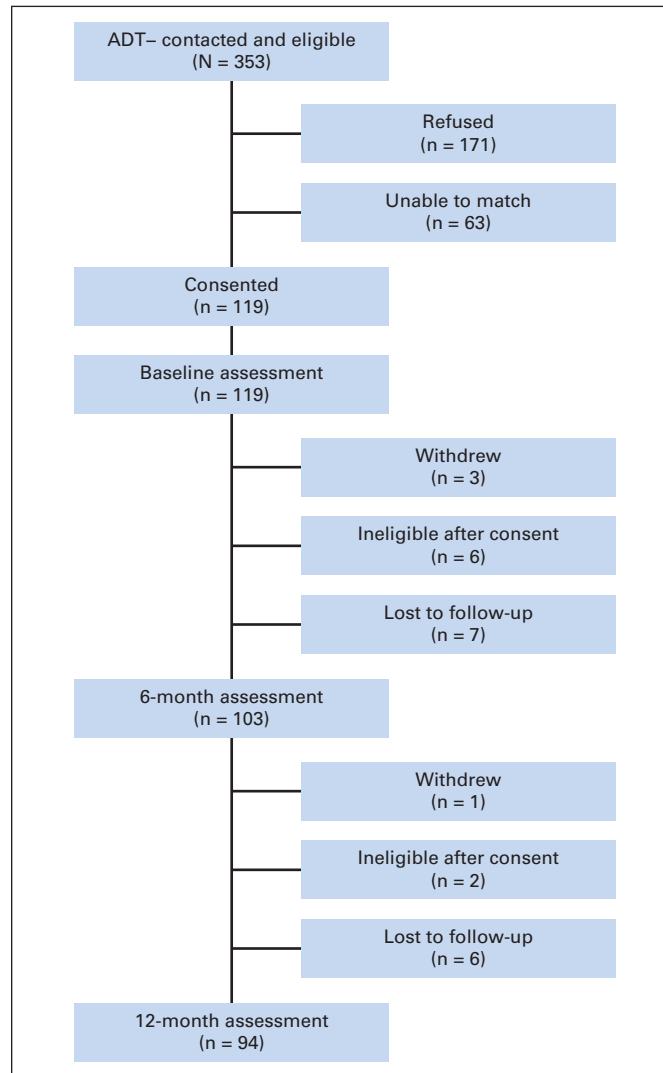
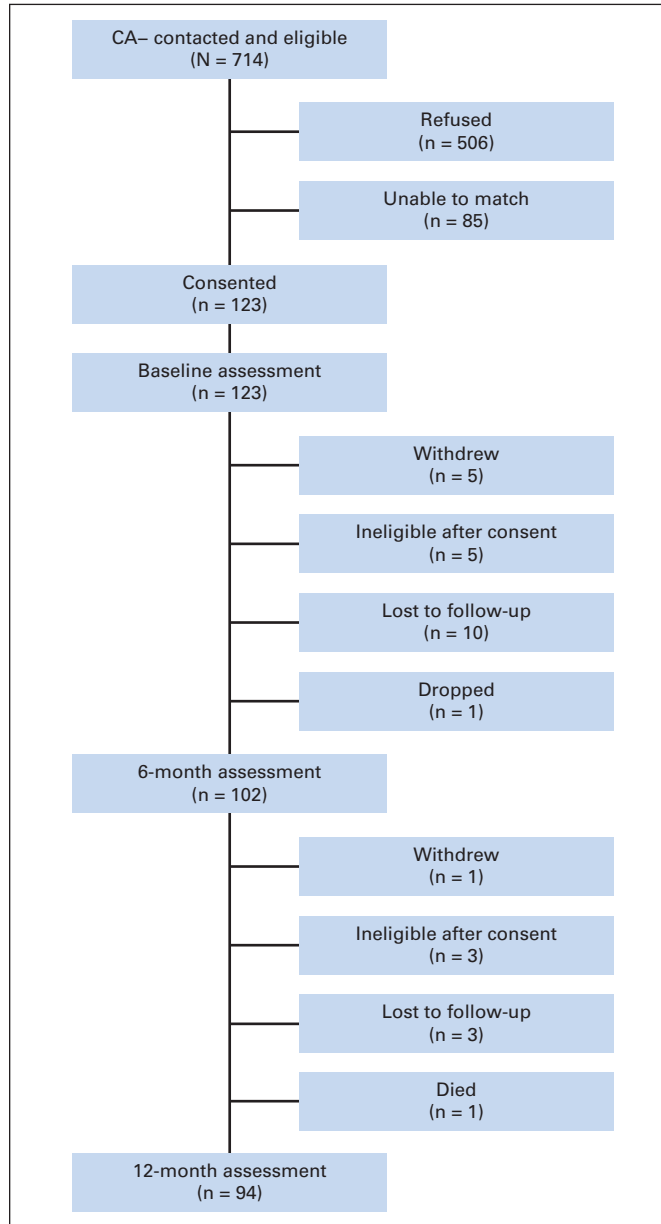


Fig A2. Participant flow for patients with prostate cancer not receiving androgen-deprivation therapy (ADT-).



**Fig A3.** Participant flow for men without prostate cancer (CA-).