Patterns of Bone Mineral Density Testing in Men Receiving Androgen Deprivation for Prostate Cancer

Vahakn B. Shahinian, MD, MS¹ and Yong-Fang Kuo, PhD^{2,3,4}

¹Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA; ²Department of Internal Medicine, University of Texas Medical Branch, Galveston, TX, USA; ³Sealy Center on Aging, University of Texas Medical Branch, Galveston, TX, USA; ⁴Department of Preventive Medicine and Community Health, University of Texas Medical Branch, Galveston, TX, USA.

BACKGROUND: Practice guidelines recommend bone mineral density (BMD) monitoring for men on androgen deprivation therapy (ADT) for prostate cancer, but single center studies suggest this is underutilized.

OBJECTIVE: We examined determinants of BMD testing in men receiving ADT in a large population-based cohort of men with prostate cancer.

DESIGN: Retrospective cohort study.

PARTICIPANTS: We used the Surveillance, Epidemiology and End-Results (SEER)-Medicare database to identify 84,036 men with prostate cancer initiating ADT from 1996 through 2008.

MAIN MEASURES: Rates of BMD testing within the period 12 months prior to 3 months after initiation of ADT were assessed and compared to matched controls without cancer and to men with prostate cancer not receiving ADT. A logistic regression model was performed predicting use of BMD testing, adjusted for patient demographics, indications for ADT use, year of diagnosis and specialty of the physician involved in the care of the patient.

KEY RESULTS: Rates of BMD testing increased steadily over time in men receiving ADT, diverging from the control groups such that by 2008, 11.5 % of men were receiving BMD testing versus 4.4 % in men with prostate cancer not on ADT and 3.8 % in the non-cancer controls. In the logistic regression model, year of diagnosis, race/ethnicity, indications for ADT use and geographic region were significant predictors of BMD testing. Patients with only a urologist involved in their care were significantly less likely to receive BMD testing as compared to those with both a urologist and a primary care physician (PCP) (odds ratio 0.71, 95 % confidence interval 0.64–0.80).

CONCLUSIONS: There has been a sharp increase in rates of BMD testing among men receiving ADT for prostate cancer over time, beyond rates noted in contemporaneous controls. Absolute rates of BMD testing remain low, however, but are higher in men who have a PCP involved in their care.

KEY WORDS: prostate cancer; osteoporosis; androgen deprivation therapy; bone mineral density.

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INTRODUCTION

Despite recent declines in use following cuts in reimbursement, androgen deprivation therapy (ADT) remains an extremely common treatment for men with prostate cancer.¹ It has long been known to be beneficial for palliation of metastatic disease, and more recently, was shown to prolong overall survival when used as an adjuvant with radiation treatment in high risk tumors.^{2–4} However, there is increasing concern about major adverse effects from ADT, particularly relating to its effects on bone.

Studies documenting reduction in bone mineral density (BMD) in men receiving ADT started accumulating in the late 1990s,^{5–7} culminating in a clinical trial of the bisphosphonate pamidronate demonstrating preservation of BMD in such men in 2001.⁸ In 2002, the first reviews recommending monitoring of men with prostate cancer on ADT with BMD testing were published.^{9–11} Those recommendations were incorporated into practice guidelines of the time,¹² following larger scale studies in 2005 and later that demonstrated an increase in fracture risk associated with use of ADT.^{13,14} Although the most recent version of the National Comprehensive Cancer Network (NCCN) guidelines provide fairly nuanced recommendations for baseline BMD testing based on risk of fracture from the FRAX algorithm endorsed by the World Health Organization, older versions suggested wider consideration of testing in all men undergoing chemical or surgical castration.^{12,15}

In single center studies, rates of BMD testing in men receiving ADT have been very low, ranging from 9 to 13 %.^{16–18} One study examining the specialty of the provider ordering the BMD test demonstrated that the majority were primary care physicians (PCPs).¹⁶ A recent population-based study done in Ontario, Canada also confirmed the very low rates of BMD testing in men on ADT.¹⁹ We therefore examined this issue in the United States using the

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Surveillance, Epidemiology and End Results (SEER)-Medicare database.

METHODS

The study protocol was approved by the institutional review board at the University of Michigan.

Data Sources

The SEER-Medicare database links two large population-based sources of data that together provide information about older adults with newly diagnosed cancer.²⁰ The SEER program is administered by the National Cancer Institute, and consists of regional and state-based tumor registries located throughout the country. It represented approximately 14 % of the United States population until 2001 and 26 % thereafter. The Medicare program provides data in the form of claims submitted by providers for reimbursement, which include information on diagnoses and the service, testing or procedure carried out. The SEER-Medicare database also provides a 5 % non-cancer control sample of Medicare beneficiaries residing in SEER regions who do not have a registered diagnosis of cancer. The American Medical Association (AMA) Physician Masterfile contains information on all physicians in the US, collected from primary sources such as medical schools, residency training programs, state licensing agencies and the American Board of Medical Specialties, in addition to surveys of physicians regarding their current hospital, practice and employment.

Study Subjects

We identified a cohort of men with a registered diagnosis in SEER of prostate cancer who initiated androgen deprivation therapy as follows. All men aged 66 years and older who for the first time received 6 months or more of gonadotropin-releasing hormone (GnRH) agonist administration, or who underwent orchiectomy, in the years 1996 through 2008 were initially selected. To ensure that ADT use was incident, a requirement was imposed that no Medicare claims for ADT were present for at least one calendar year prior to the year of first use. To ensure complete information, those not continuously enrolled in both Medicare Part A and Part B for 12 months prior to and 3 months following the first use of ADT, who were members of an Health Maintenance Organization, or had their cancer diagnosed by autopsy or death certificate were excluded, leaving 84,036 eligible subjects for the primary analysis of factors predicting use of BMD testing among men receiving ADT.

For the analysis of time trends in use of BMD testing only, we also assembled two matching control cohorts, one consisting of men with prostate cancer who did not receive ADT, and the other consisting of men without a registered diagnosis of cancer in SEER (from the 5 % non-cancer sample). This was done by selecting men for study entry matched on age at diagnosis of prostate cancer (categorized as 66–69, 70–74, 75–79, 80–84, and ≥ 85 years old), SEER region of residence (categorized as Northeast, Midwest, South, and West), and quarter of the calendar year of diagnosis of prostate cancer. Random selection was performed if more than one match was available. Successful matching was possible in 100 % of cases for calendar year, 97.6 % for age and 95.3 % for region from the non-cancer controls and in 100 % of cases for calendar year, 94.8 % for age and 90.6 % for region from the prostate cancer without ADT cohort.

Study Definitions

The primary outcome was whether men received bone mineral density testing, either through dual x-ray absorptiometry or quantitative computed tomography (QCT) scanning, defined as the presence of a Medicare claim for at least one of the following codes: International Classification of Diseases, 9th revision (ICD9) code 88.98, or Current Procedural Terminology (CPT) 76070, 76071, 76075, 76076, 76077, 76078, 77078, 77079, 77080, 77081, 77082, 77083, 76977, 78350, 78351, G0131, G0132, G0062, or G0063. For the main analyses, we focused on whether baseline BMD testing was performed, which we defined as occurring within the period 12 months prior to 3 months after ADT was initiated because published recommendations^{9–12} suggest performing a baseline examination prior to initiation of ADT. We also examined a second period from 3 months prior to 18 months following initiation of ADT to capture use of follow-up BMD monitoring for patients on ADT ($n=72,840$). In additional analyses, we assessed use of treatment for osteoporosis in men undergoing BMD testing. We were limited to examination of Medicare claims for injectable medications based on the relevant J codes. These included claims for teriparatide (J3110), denosumab (J0897) and the intravenously given bisphosphonates pamidronate, zoledronic acid, etidronate and ibandronate (J2430, J3487, J1436 and J1740).

Use of ADT, either in the form of GnRH agonists or orchiectomy, was identified from Medicare claims based on previously developed and published algorithms.¹³ Demographic information on patient age (categorized as 66–74 years, 75–84 years, or ≥ 85 years), SEER region of residence (categorized as Northeast, Midwest, South, or West) and race/ethnicity (categorized as non-Hispanic White, non-Hispanic Black, Hispanic, or other) were obtained from SEER records. Comorbidity was measured using an adaptation of the

Charlson Comorbidity Index for use with Medicare physician claims data.^{21,22} We also defined a variable designating indications for use of ADT. This was divided into three categories: primary ADT (defined as use of ADT within 12 months of cancer diagnosis in the absence of other therapies), adjuvant ADT (defined as use of ADT within 12 months of cancer diagnosis in combination with radical prostatectomy or radiation treatment) and delayed ADT (defined as initiation of ADT beyond 12 months of diagnosis). We hypothesized there would be a higher rate of BMD testing in the delayed ADT group (usually given either for progression or recurrence of disease), as it would likely include patients provided a prolonged duration of ADT. Physicians involved in the care of patients were identified based on the presence of at least one outpatient physician claim (excluding emergency room visits) in the 12 months prior to initiation of ADT, indicating a face-to-face visit (Evaluation and Management codes of the form 99XXX). The unique physician identifier number (UPIN) was linked to AMA data to obtain specialty of the physician, categorized as PCP (general practice, family practice, general internal medicine or geriatrics), oncologist (radiation oncologist or medical oncologist), urologist, or other (specialty information was missing for 158 physicians). The specialty of the physician ordering the BMD test was also obtained by using the UPIN from the "referring UPIN number" field in the physician claim associated with the BMD test (the field was blank in 215 patients).

Statistical Analyses

The proportion of patients receiving a BMD test among those men initiating ADT for each calendar year was calculated and plotted alongside values for men in the two control groups: those with prostate cancer not receiving ADT, and those without prostate cancer from the 5 % non-cancer control population. The proportion of men receiving a BMD test was also stratified by patient age, race/ethnicity, SEER region, comorbidity, indication for use of ADT, and specialty of physician. Chi-square statistics were used to assess differences across categories for each variable above. A multivariable logistic regression model was also performed for the outcome of BMD testing, with the above characteristics plus year of incident ADT use entered as independent variables. Two-way interactions between indications for ADT use and each characteristic were tested in the multivariable logistic regression model. For each variable, odds ratios with associated 95 % confidence intervals (CI) were calculated. Analyses were performed using SAS v.9.3 (SAS institute, Cary, NC) with all tests being two-sided and $p < 0.05$ considered statistically significant.

RESULTS

A total of 84,036 men with prostate cancer initiated ADT from 1996 through 2008. Figure 1 presents a plot by year of the proportion of those men receiving baseline BMD testing (within a window of 12 months prior to 3 months following initiation of ADT), together with plots of matched controls with prostate cancer not initiating ADT and men without cancer. Receipt of BMD testing increased over time in all three groups, but with a sharp rise in the group receiving ADT starting in 2002, diverging from the curves for the matched control groups. By 2008, 11.5 % of men initiating ADT were receiving BMD testing versus 4.4 % in men with prostate cancer not initiating ADT and 3.8 % in the non-cancer controls. Figure 2 presents a similar plot for receipt of follow-up BMD testing (within a period extending from 3 months after to 18 months after initiation of ADT). As for Figure 1, there is a steady increase in use of BMD testing over time, but the curve for men receiving ADT diverges earlier from the control groups, in 1998, and plateaus at around 11 % from 2005 onwards.

Table 1 presents the proportion of men receiving baseline and follow-up BMD testing, stratified by patient characteristics. Rates of follow-up testing were somewhat higher, but the pattern of results was similar for both baseline and follow-up testing, with men of non-Hispanic Black race/ethnicity, those with a comorbidity index of zero, and those being cared for by only a urologist, having the lowest rates of BMD testing. Of patients receiving a baseline BMD test, 22.6 % also received a follow-up test, for an overall proportion of 4.1 % of men initiating ADT receiving both baseline and follow-up testing.

Figure 1. Proportion of men with prostate cancer receiving a bone mineral density test within the period 12 months prior to 3 months after initiation of androgen deprivation therapy, plotted by year (blue circles). Also plotted are the proportion of men receiving a bone mineral density test in matched cohorts consisting of men with prostate cancer not receiving androgen deprivation (yellow squares) and men without cancer (green triangles). BMD bone mineral density, ADT androgen deprivation therapy.

Figure 2. Proportion of men with prostate cancer receiving a bone mineral density test within the period 3 months after to 18 months after initiation of androgen deprivation therapy, plotted by year (blue circles). Also plotted are the proportion of men receiving a bone mineral density test in matched cohorts consisting of men with prostate cancer not receiving androgen deprivation therapy (yellow squares) and men without cancer (green triangles). BMD bone mineral density, ADT androgen deprivation therapy.

Table 2 presents the results of a logistic regression model examining predictors of baseline and follow-up BMD testing among men initiating ADT. The results were similar for both baseline and follow-up testing. There is an increase in BMD testing over time, with a 10-fold to 20-fold rise in

the odds of testing in 2008 compared with 1996. Patients of non-Hispanic Black, or Hispanic race/ethnicity were significantly less likely to receive BMD testing as compared with non-Hispanic Whites. Men receiving delayed ADT had a slightly higher odds of BMD testing as compared with men receiving primary or adjuvant ADT within 12 months of cancer diagnosis. There was also significant geographic variation in the likelihood of BMD testing, with the lowest odds in the South and the highest in the Western regions. Finally, the specialty of the physician involved in the care of the patient was a significant predictor of BMD testing. Patients receiving care by a urologist, with or without additional involvement of a PCP or oncologist, were significantly less likely to receive BMD testing as compared with patients receiving care by PCPs or oncologists. In an additional analysis examining the specialty of the physicians ordering the baseline BMD tests ($n=3,278$), the majority (51.3 %) were ordered by PCPs, followed by urologists (17.9 %) and oncologists (11.3 %). The remaining tests were ordered by a variety of specialties, including rheumatologists and endocrinologists. Use of injectable treatments for osteoporosis within 12 months of the baseline BMD test was also examined. Over the entire study period, 7.9 % of patients receiving a BMD test also received treatment. There was a steady increase over time, with 3.4 % receiving treatment over the period 1996 through 2000, versus 8.5 % over the period 2005 through 2008.

Table 1. Characteristics of Patients Receiving Bone Mineral Density Testing Among Men with Prostate Cancer Initiating Androgen Deprivation Therapy

Characteristics	Category	Proportion receiving baseline BMD test				Proportion receiving follow-up BMD test			
		Total ADT users	n	%	p value	Total ADT users	n	%	p value
Age (years)	66–74	30884	1244	4.03	0.084	27825	1908	6.86	< 0.001
	75–84	41771	1818	4.35		36277	2568	7.08	
	≥ 85	11381	493	4.33		8738	505	5.78	
Race/ethnicity	Non-Hispanic White	66750	2796	4.19	< 0.001	58101	3946	6.79	< 0.001
	Non-Hispanic Black	7743	213	2.75		6521	281	4.31	
	Hispanic	4056	189	4.66		3421	242	7.07	
SEER region	Other/Unknown	5487	357	6.51	< 0.001	4797	512	10.67	< 0.001
	Northeast	19736	696	3.53		17558	1003	5.71	
	Midwest	19223	597	3.11		16817	967	5.75	
	South	10392	296	2.85		9035	451	4.99	
	West	34685	1966	5.67		29430	2560	8.70	
Indications for ADT	Primary ADT	26362	1031	3.91	< 0.001	24592	1679	6.83	0.106
	Adjuvant ADT	26515	1027	3.87		22598	1488	6.58	
	Delayed ADT	31159	1497	4.80		25650	1814	7.07	
Comorbidity index	0	53699	2104	3.92	< 0.001	47850	3131	6.54	< 0.001
	1	19014	912	4.80		16193	1222	7.55 %	
	2	6975	317	4.54		5617	403	7.17	
	≥3	4348	222	5.11		3180	225	7.08	
Physician involved in care	Urologist only	13828	385	2.78	< 0.001	56183	3937	7.01	< 0.001
	Urologist + (PCP or oncologist)	64685	2751	4.25		12341	617	5.00	
	PCP only	1711	108	6.31		2230	264	11.84	
	Oncologist (with or without PCP)	2946	284	9.64		1360	106	7.79	
	Other	866	27	3.12		726	57	7.85	

ADT androgen deprivation therapy; BMD bone mineral density; SEER surveillance, epidemiology and end-results; PCP primary care physician

DISCUSSION

In a large population-based sample of men with prostate cancer, this study confirms a sharp increase over time in rates of BMD testing for those initiating ADT. The divergence from rates of BMD testing in prostate cancer controls not receiving ADT or from non-cancer controls implies specific attention to concerns about bone disease related to ADT raised by studies in the late 1990s and later. However, absolute rates of testing remained quite low, at approximately 11 %, even in recent years.

What may explain the low rates of BMD testing? First, most of the recommendations for BMD monitoring in men on ADT stem from reviews, with essentially only one set of

formal practice guidelines, from the NCCN, addressing this specific issue. It is already well documented that physicians are often slow to adopt practice guidelines for a number of reasons,²³ and in this context the evidence underlying the recommendations is weak. Various agents have been shown in clinical trials to help preserve or even improve BMD,^{8,24,25} and a decision analysis suggested that a strategy involving BMD testing at initiation of ADT, coupled with bisphosphonate therapy if osteoporosis was present, was cost effective.²⁶ Nevertheless, conclusive evidence from clinical trials for the ability of these agents to reduce fracture outcomes is currently still lacking,²⁷ likely raising doubts in clinicians' minds about the utility of

Table 2. Odds of Receiving Bone Mineral Density Testing Among Patients Initiating Androgen Deprivation Therapy for Prostate Cancer

Characteristics	Category	Receipt of baseline BMD testing		Receipt of follow-up BMD testing	
		Odds ratio*	95 % confidence interval	Odds ratio†	95 % confidence interval
Year of incident ADT use	1996	1.00	Reference	1.00	Reference
	1997	2.03	1.18,3.49	1.38	0.95, 2.00
	1998	3.60	2.18,5.96	2.72	1.97, 3.79
	1999	5.14	3.15,8.237	2.98	2.15, 4.13
	2000	5.47	3.40,8.80	3.63	2.66, 4.95
	2001	7.74	4.85,12.36	4.63	3.41, 6.28
	2002	10.53	6.63,16.73	6.17	4.56, 8.33
	2003	11.09	6.98,17.61	7.44	5.52, 10.04
	2004	14.56	9.19,23.06	9.43	7.00, 12.69
	2005	17.34	10.93,27.52	10.12	7.49, 13.66
	2006	20.32	12.81,32.22	9.62	7.11, 13.01
	2007	21.76	13.67,34.64	11.25	8.28, 15.27
Indication for ADT	2008	24.05	15.08,38.36	9.25	6.50, 13.18
	Adjuvant	1.00	Reference	1.00	Reference
	Primary	1.00	0.94,1.05	1.01	0.97, 1.06
Age (for every 5 years)‡	Delayed	1.10	1.05,1.16	1.07	1.02, 1.12
	Adjuvant ADT	1.11	1.04,1.18	1.02	0.97, 1.07
	Primary ADT	0.98	0.93,1.03	0.94	0.90, 0.98
Race/ethnicity	Delayed ADT	0.95	0.91,0.98	0.89	0.86, 0.93
	Non-Hispanic White	1.00	Reference	1.00	Reference
	Non-Hispanic Black	0.68	0.58,0.78	0.62	0.55, 0.71
	Hispanic	0.81	0.69,0.95	0.80	0.69, 0.91
SEER region	Other/Unknown	1.16	1.03,1.31	1.28	1.15, 1.41
	Northeast	1.00	Reference	1.00	Reference
	Midwest	0.99	0.89,1.11	1.19	1.08, 1.30
	South	0.78	0.68,0.90	0.85	0.76, 0.96
Comorbidity index	West	1.62	1.48,1.78	1.65	1.52, 1.78
	0	1.00	Reference	1.00	Reference
	1	1.19	1.09,1.29	1.14	1.07, 1.23
	2	1.08	0.96,1.22	1.06	0.95, 1.18
Physician involved in care	≥ 3	1.15	1.00,1.33	1.01	0.87, 1.16
	Urologist + (PCP or oncologist)	1.00	Reference	1.00	Reference
	Urologist only	0.71	0.64,0.80	0.77	0.70, 0.84
	Oncologist (with or without PCP)	1.70	1.48,1.94	1.42	1.24, 1.64
	PCP only	1.23	1.00,1.51	1.02	0.83, 1.26
	Other	0.71	0.48,1.05	1.20	0.91, 1.59

*Based on a multivariable logistic regression model with receipt of bone mineral density testing within 12 months prior to 3 months after initiation of androgen deprivation therapy as the dependent variable, and age at initiation of androgen deprivation, year of initiation of androgen deprivation, SEER region, comorbidity index, race/ethnicity, indication for ADT use, and specialty of physician involved in care of patient entered as independent variables

†Based on a multivariable logistic regression model with receipt of bone mineral density testing within 3 months after to 18 months after initiation of androgen deprivation therapy as the dependent variable, and age at initiation of androgen deprivation, year of initiation of androgen deprivation, SEER region, comorbidity index, race/ethnicity, indication for ADT use, and specialty of physician involved in care of patient entered as independent variables

‡The interaction between age and indication for ADT use on the outcome of receipt of bone mineral density testing was significant ($p < 0.001$) so stratified results are presented. Interactions between indication for ADT use and other variables were not significant.
ADT androgen deprivation therapy; SEER Surveillance, epidemiology and end results; PCP primary care physician

measuring BMD. Perhaps reflecting these uncertainties, recent versions of the NCCN guidelines provide more refined recommendations regarding for whom BMD testing should be performed, based on a formal assessment of fracture risk.

Reimbursement for BMD testing may have also affected its use. Medicare reimbursement for BMD testing was initiated in 1999, did not explicitly include an indication for use in men on ADT, and was limited to testing once every 2 years. Although medical exceptions for the preceding restrictions are possible, this may nevertheless have presented barriers to use of testing for men receiving ADT.²⁸ One national study of Medicare claims demonstrated denial of claims for BMD testing in 9.1 % of cases for men overall, and up to 42 % by some Medicare carriers for repeat testing done more frequently than 2 years.²⁹ There was also substantial variation in denial rates by region, which may in part explain the regional variation we noted in this study in rates of BMD testing.

An important factor influencing BMD testing in our study was the specialty of the physicians involved in the care of the patient. The inclusion of a PCP significantly increased the likelihood of testing as compared to a scenario in which only a urologist was involved. Furthermore, although we have previously documented that urologists are responsible for prescribing the vast majority of ADT,³⁰ PCPs appear to order a majority of the BMD tests. This is perhaps not surprising, as bone health does not fall under the usual purview of urologic care, and many urologists may not feel comfortable diagnosing and managing osteoporosis. Our findings parallel studies of breast and colorectal cancer patients, which have shown that the involvement of a PCP in addition to an oncologist increases the use of general preventive medical services.^{31,32} Recognizing the importance of appropriate sharing of care between PCPs and cancer specialists, the Institute of Medicine has proposed the use of survivorship care plans.³³ These include documentation of ongoing surveillance needs for adverse effects of cancer therapy, as well as designation of the appropriate providers for each aspect of care. Our study findings support the need to find ways to ensure that PCPs are adequately involved in the care of men with prostate cancer receiving ADT. This may not only help improve management of bone disease, but also other adverse effects of ADT such as cardiovascular disease, diabetes mellitus and hyperlipidemia, which may all be most appropriately addressed by PCPs.

There are important limitations to this study. Since it includes only Medicare patients, the results are limited to the examination of men 65 years or older. Patterns of BMD testing may be different in younger populations of men. The identification of BMD testing was based on Medicare claims alone, which may be subject to misclassification. However, the BMD testing rates we note are similar to

contemporaneously conducted single center studies which used chart review.^{16–18} Some of the BMD testing may have been done for work-up of pathologic fractures related to metastatic disease, rather than for the purposes of monitoring men on ADT. Finally, the rate of treatment for osteoporosis following BMD testing was likely an underestimate as we were limited to examining use of injectable medications, and would have missed prescribed oral agents.

In summary, this study documents a sharp increase in rates of BMD testing among men receiving ADT for prostate cancer over time, beyond rates noted in contemporaneous control groups of men without cancer or men with prostate cancer not receiving ADT. Absolute rates of BMD testing remain low, however, but are higher in men who have a PCP involved in their care.

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Conflict of Interest: Dr. Shahinian is a paid consultant for Amgen, Inc.

Corresponding Author: Vahakn B. Shahinian, MD, MS; Department of Internal Medicine, University of Michigan, 1415 Washington Heights, Room 3627, SPH I, Ann Arbor, MI 48109-2029, USA (e-mail: vahakn@umich.edu).

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