

Mail-Order Pharmacy Use and Adherence to Diabetes-Related Medications

O. Kenrik Duru, MD, MSHS; Julie A. Schmittiel, PhD; Wendy T. Dyer, MSc; Melissa M. Parker, MS; Connie S. Uratsu, MS; James Chan, PharmD; and Andrew J. Karter, PhD

Although recent scientific breakthroughs have produced medications that improve outcomes for chronic conditions, there has not been a corresponding improvement in medication adherence.^{1,2} Although better adherence is associated with fewer hospitalizations and lower mortality in patients with diabetes mellitus,³⁻⁵ half of the patients who are prescribed medications for chronic conditions such as diabetes discontinue them after several years. Of patients who continue taking these medications, only 50% to 70% achieve good adherence,^{1,6,7} in part because of various patient-level, provider-level, and system-level obstacles.^{8,9} Patient-system interactions such as medication refills are also important determinants of medication adherence. Successful and timely refills are not a guarantee of medication consumption, but they represent a minimum step necessary to ensure good adherence.

The use of mail-order pharmacies may streamline the refill process because mailed medications eliminate the need for travel to the pharmacy. Home delivery may be particularly beneficial for patients with disabilities, inadequate access to transportation, or time constraints.¹⁰ Patients who use mail-order pharmacies purchase more medications than patients using local walk-in pharmacies.¹¹⁻¹³ However, this difference could represent factors other than better adherence such as self-selection into mail order by adherent patients. In addition, most mail-order pharmacies mandate that patients purchase a 90-day medication supply, unlike local pharmacies. Medication purchases by mail-order users may not reflect actual adherence if providers alter the regimen after 30 to 60 days and patients are obligated to waste pills.¹³ Although one-third of chronic disease prescriptions in the United States are filled by mail,¹⁴ there has been little evaluation of patients' propensity to use mail-order pharmacies or whether the use of mail-order pharmacies is associated with medication adherence.

Among patients with diabetes in an integrated delivery system, we examined (1) the demographic and clinical factors associated with the use of mail-order pharmacies and (2) the likelihood of good adherence to newly prescribed antiglycemic, antihypertensive, and lipid-lowering medications, comparing mail-order pharmacy users with local pharmacy users. We used a data set in which the days' supply is similar for mail-order and local pharmacies, and we used statistical techniques to assess for selection bias. We hypothesized that

Objective: To investigate whether patients who use mail-order pharmacies were more likely to have good medication adherence than patients who use local pharmacies.

Study Design: Cross-sectional investigation.

Methods: We conducted cross-sectional analyses of patients from the Kaiser Permanente Northern California (KPNC) diabetes registry who received a new antiglycemic, antihypertensive, or lipid-lowering index medication between January 1, 2006, and May 31, 2006. We defined good adherence as medication availability at least 80% of the time (ie, a continuous measure of medication gaps value of $\leq 20\%$) and compared adherence between mail-order users ($\geq 66\%$ of refills by mail) and KPNC local pharmacy users (all refills in person). Adherence was calculated from the initial dispensing through 15 months of follow-up, medication discontinuation, or May 31, 2007, whichever came first. We analyzed the data using multivariate logistic regression models, after determining that unmeasured patient-level factors and self-selection did not significantly bias our analyses.

Results: A total of 13,922 eligible patients refilled an index medication. Compared with those who used only local KPNC pharmacies, patients who received medications by mail were more likely to have good adherence (84.7% vs 76.9%, $P < .001$). After adjusting for potential confounders, including days' supply and out-of-pocket costs, mail-order users had better adherence to antiglycemic, antihypertensive, and lipid-lowering medications ($P < .001$ for all).

Conclusions: Compared with patients who obtained medication refills at local pharmacies, patients who received them by mail were more likely to have good adherence. The association between mail-order use and medication adherence should be evaluated in a randomized clinical trial.

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Take-Away Points

In this study of an integrated delivery system, the use of mail-order pharmacies was associated with a higher likelihood of good medication adherence.

- Minority patients and patients of low socioeconomic status were less likely to refill their medications by mail.
- Although these findings should be confirmed in other analyses and in a randomized controlled trial, they suggest the intriguing potential of organization-level interventions to improve adherence, particularly among vulnerable populations, by promoting increased mail-order use.

patients who used a mail-order pharmacy would be more likely to have good medication adherence over a 12-month period compared with patients who used only local pharmacies.

METHODS

We conducted this study within Kaiser Permanente Northern California (KPNC), a fully integrated health system that provides comprehensive medical care to more than 3 million members. The KPNC membership includes employed persons and retirees and approximates the general population of northern California racially/ethnically and socioeconomically. The study protocol was approved by the KPNC Institutional Review Board. We selected subjects from the KPNC diabetes registry, established in 1993.¹⁵ The registry is updated annually by adding patients with diabetes identified from automated databases of pharmacy data, laboratory data, hospitalization records, and outpatient diagnoses.

Kaiser Permanente Northern California has more than 120 local walk-in pharmacies, located on-site within outpatient clinics and hospital facilities. We identified each patient's clinic and local pharmacy based on his or her prior utilization or the utilization patterns of other patients in the same zip code.¹⁶ Since 1999, KPNC has maintained a mail-order pharmacy distribution system, in coordination with local KPNC pharmacies. After completing a simple enrollment process, patients can obtain medications by mail. Although most new prescriptions are filled in the local pharmacy, KPNC patients also have the option of filling new prescriptions by mail, with telephone access to a pharmacist to answer any medication-related questions. There is no minimum days' supply required for mail-order delivery at KPNC, which typically dispenses 100-day medication supplies through mail-order and local KPNC pharmacies. Some patients have a financial incentive to use mail order, typically a lower copayment for the same days' supply obtained by mail versus at a local KPNC pharmacy.

Study Design and Participants

From the diabetes registry, we selected a subset ($n = 23,488$) of patients who were aged at least 18 years by January

1, 2006; had a pharmacy benefit; and had been prescribed a new diabetes-related medication (no recorded use in the previous 24 months) between January 1, 2006, and May 31, 2006. To most accurately estimate pharmacy utilization, we excluded members who lacked drug benefits during the study period and had little incentive to use KPNC pharmacies (approximately 4% of patients). Diabetes-related medications included antiglycemic, antihypertensive, or lipid-lowering medications. If patients were prescribed multiple new diabetes-related medications during this period, the earliest prescription was defined as the index medication. We estimated adherence for this medication using a cross-sectional study design (described herein). The study window started at the initial dispensing and continued for 15 months, until discontinuation of the medication, or until May 31, 2007, whichever came first. Patients were considered to have discontinued their medication if they did not obtain a refill within 90 days after their existing supply had run out.

Variables

To assess adherence to the index medication, we used a pharmacy utilization-based measure of secondary adherence, the continuous measure of medication gaps (CMG).¹⁷⁻¹⁹ The CMG uses refill data to determine the cumulative period for which no medication was available to the patient (gaps), dividing the number of days for which the patient did not have the medication by the number of days in the study window for that participant. The CMG values range from 0% (completely adherent) to 100% (completely nonadherent). We dichotomized CMG values, classifying values of 20% or less as good and greater than 20% as inadequate. This cutoff has been used in previous studies³⁻⁵ that examined the relationship between medication adherence and hospitalizations and mortality rates. Because the CMG cannot be calculated without at least 1 complete refill interval, we excluded 5613 patients who did not fill their prescription at least twice. The CMG cannot be reliably calculated for insulin given the flexible dosing instructions, so we also excluded 658 patients whose index medication was insulin. Patients with oral index medications who were taking insulin concurrently were not excluded.

We defined 2 patient groups for our analytic comparisons: mail-order users and local pharmacy users. Because the proportion of patients using mail-order exclusively was small (<2% of the sample), we considered patients to be mail-order users ($n = 2595$) if they used this system predominantly ($\geq 66\%$ of refills by mail). Local pharmacy users ($n = 11,327$)

obtained all their index medication refills in person. Patients who used mail-order intermittently (1%-65% of refills [$n = 3295$]) were excluded from the analysis.

We included several demographic characteristics in our analyses, including race/ethnicity (non-Latino white, African American, Latino, Asian/Pacific Islander, Native American, mixed race/ethnicity, and missing race/ethnicity). As a contextual measure of socioeconomic status, we used a neighborhood deprivation index²⁰ based on principal components analysis of the following 8 census tract variables from the 2000 US Census: percentage of households in poverty, percentage of households receiving public assistance, percentage of female-headed households with children, percentage of households earning less than \$30,000 annually, percentage with less than a high school education, percentage in crowded housing (>1 person per room), percentage unemployed, and percentage of men in management or professional occupations. The socioeconomic deprivation score was standardized to a mean (SD) of 0 (1), with negative scores indicating less deprived neighborhoods.

The number of comorbid conditions for each patient was ascertained from the KPNC outpatient clinical records database for the 18 months before the first refill. Patients were classified by their type of insurance (non-Medicare commercial, Medicare Part D with a group insurer, or Medicare Part D from the individual insurance market) and by whether they had a financial incentive to order by mail. We calculated the linear distance from the patient's home address to his or her local KPNC pharmacy using MapMarker geocoding software (Pitney Bowes MapInfo, Troy, NY). We categorized the days' supply of the index medication dispensed at the first refill into 1 to 30, 31 to 60, 61 to 90, or more than 90 days. Finally, we measured the duration of therapy for the index medication, defined as the number of days from the first fill through the last fill before discontinuation or the end of the study window.

Statistical Analysis

We estimated separate logistic regression models using Stata version 9.2 (StataCorp LP, College Station, TX) to examine (1) variables associated with mail-order pharmacy use and (2) differences in the probability of good medication adherence between mail-order and local pharmacy users. In each analysis, we included the following as covariates: age; sex; race/ethnicity; neighborhood socioeconomic deprivation score; number of comorbidities; smoking status; use of nonformulary medications, antidepressants, or insulin; insurance type; financial incentive to order by mail; distance from the patient's home to the local pharmacy; an indicator for whether the index medication was generic or brand name; length of therapy with the index medication; and medical

facility dummy variables. To facilitate interpretability of the results, we estimated predicted percentages (95% confidence intervals) for groups of interest, holding all other covariates at their mean value.

Observational studies are susceptible to more bias than experimental ones when studying causal relationships. Omitted (unmeasured) variable bias, or self-selection (eg, differences in intrinsic patient motivation to use mail order), is of particular concern in this study. We used health econometric techniques, specifically a bivariate probit (BVP) model incorporating an instrumental variable, to assess whether our estimates from the logistic regression predicting medication adherence were subject to omitted variable bias. A nonlinear BVP model is more appropriate than a standard linear instrumental variable model when the outcome (eg, medication adherence) and the treatment variable (eg, mail-order pharmacy use) are binary.^{21,22}

We used distance from the patient's home to his or her local pharmacy as our instrumental variable in the BVP model based on empirical evidence and theoretical considerations.^{23,24} Greater distance was associated with a greater likelihood of mail-order pharmacy use in unadjusted analyses ($\chi^2 = 78.48, P < .001$). In addition, distance was not independently associated with medication adherence or other variables such as age, sex, socioeconomic status, and number of comorbidities. The lack of association between our instrument and these observed variables suggests that it is also independent of other correlated but unobserved variables, although this relationship cannot be directly tested. Finally, multiple health services research studies²⁵⁻²⁸ have used distance to healthcare facilities as an instrument.

The likelihood ratio test in the BVP model was nonsignificant ($P = .94$), and the observed effect size was similar to the logistic regression model. Because the likelihood ratio test did not provide evidence of omitted variable bias, we elected to report results from the more efficient logistic regression analysis rather than the BVP model.

RESULTS

The final analytic sample included 13,922 patients with diabetes who had been recently prescribed an antiglycemic, antihypertensive, or lipid-lowering medication and filled the prescription at least twice (Table 1). Compared with local KPNC pharmacy users, mail-order pharmacy users were more likely to be non-Latino white (61.0% vs 37.1%) and in the least deprived socioeconomic status quartile (27.5% vs 17.8%) ($P < .001$ for both). Compared with local pharmacy users, mail-order pharmacy users were more likely to have a financial incentive to fill their prescriptions by mail (49.6% vs

■ **Table 1.** Unadjusted Patient Characteristics by Pharmacy Type

Characteristic	Entire Sample (N = 13,922)	Mail-Order Pharmacy Users (n = 2595)	Local Pharmacy Users (n = 11,327)	P Value for Unadjusted Difference Between Mail-Order and Local Pharmacy Users
Demographics				
Female sex, %	46.2	44.2	46.7	.02
Age, mean (SD), y	62 (11.9)	64 (11.2)	62 (12.0)	<.001
Race/ethnicity, %				
White, non-Latino	41.6	61.0	37.1	<.001
African American	9.9	3.1	11.4	<.001
Latino	9.2	4.8	10.2	<.001
Asian/Pacific Islander	11.2	9.3	11.6	.001
Native American	1.6	1.7	1.6	.75
Mixed race/ethnicity	11.3	8.6	12.0	<.001
Missing race/ethnicity	15.3	11.6	16.1	<.001
Distance from home to the local pharmacy, mean (SD), miles	6.9 (10.1)	8.0 (12.5)	6.7 (9.5)	<.001
Socioeconomic deprivation score quartile, %				
1, Least deprived	19.6	27.5	17.8	<.001
2	28.6	30.0	28.3	.10
3	26.8	22.8	27.8	<.001
4, Most deprived	19.0	10.6	21.0	<.001
Missing socioeconomic data	5.9	9.2	5.2	<.001
Clinical Characteristics				
No. of comorbidities, mean (SD)	0.80 (1.0)	0.82 (1.0)	0.80 (1.1)	.45
Smoker, %	7.7	6.6	8.0	.02
Use of antidepressant, %	21.5	23.0	21.1	.03
Use of insulin, %	19.1	16.3	19.8	<.001
Use of nonformulary medication, %	5.8	6.1	5.8	.49
New medication is brand name, %	22.1	25.3	21.4	<.001
Medication days' supply, %				
1-30	4.8	2.7	5.3	<.001
31-60	5.1	4.0	5.4	.003
61-90	5.6	6.5	5.4	.04
>90 days	84.4	86.9	83.9	<.001
No. of days from first medication fill to last fill, mean (SD) ^a	347 (101.3)	371 (75.7)	341 (105.6)	<.001
Insurance Type, %				
Medicare Part D group	18.4	14.2	19.4	<.001
Medicare Part D individual	18.2	29.7	15.6	<.001
Commercial non-Medicare	63.3	56.0	65.0	<.001
Financial incentive to order by mail	28.0	49.6	23.0	<.001

^aLast medication fill is the last fill before discontinuation (defined as ≥90 days without a refill) or the last fill before the end of the study window.

23.0%) and had a greater mean distance from their home to the local pharmacy (8.0 vs 6.7 miles) ($P < .001$ for both).

After multivariate adjustment, characteristics associated with mail-order pharmacy use were largely unchanged. Holding all other covariates constant at their mean, the predicted probabilities of mail-order pharmacy use did not differ by patient sex, age, or number of comorbidities (Table 2). However, non-Latino white patients were predicted to have a higher likelihood of mail-order use (24.1%) than African Americans (4.0%), Latinos (5.2%), Asian/Pacific Islanders (8.4%), and patients of mixed race/ethnicity (8.0%) ($P < .001$ for all). Twenty-one percent of patients living in the least deprived neighborhoods were predicted to refill their medications by mail compared with 12.1%, 10.8%, and 8.4% ($P < .001$ for all) of patients in progressively more deprived neighborhood quartiles. Patients living at least 4 miles from their local pharmacy were predicted to refill their new medications by mail more often than patients living less than 4 miles from their local pharmacy (16.5% vs 13.3%, $P < .001$). Patients with a financial incentive to use the mail-order pharmacy had a substantially greater predicted probability of using mail order compared with patients with no incentive (35.3% vs 10.1%, $P < .001$).

In adjusted models, patients who filled any new prescription by mail were 7.8 percentage points more likely to have good adherence compared with those who used local pharmacies (84.7% vs 76.9%, $P < .001$) (Table 3). Separate models for antidiabetic medications (difference of 6.6 percentage points), antihypertensive medications (difference of 7.7 percentage points), and lipid-lowering medications (difference of 9.3 percentage points) ($P < .001$ for all) gave similar results.

DISCUSSION

Our analysis is one of the first studies to examine the characteristics of patients using mail-order pharmacies. It confirmed that patients who received newly prescribed medications through the mail were more likely to have good adherence than patients who obtained them at local KPNC pharmacies. Although there is a paucity of literature in this area, our findings of a 7- to 8-percentage point increase in good adherence associated with mail-order use are consistent with a recent industry non-peer-reviewed study.²⁹ That study compared adherence within a health plan that required members to use a mail-order pharmacy and another plan that required members to use a local pharmacy. The authors found that, compared with the use of a local pharmacy, the use of a mail-order pharmacy was associated with an 8.4-percentage point increase in good adherence to antidiabetic medications, a 7.8-percentage point increase in good adherence

to antihypertensive medications, and a 6.8-percentage point increase in good adherence to lipid-lowering medications.

Inferences from observational studies are limited by biases not evident in randomized exposures. Self-selection is of particular concern when studying outcomes such as medication adherence because it may introduce unmeasured differences in patient characteristics. These characteristics could potentially be associated with adherence and result in spurious associations between adherence and pharmacy type. The results of the likelihood ratio test within a BVP model suggest that unmeasured patient self-selection into mail order did not significantly distort our findings. We also controlled for potential confounders not addressed in prior published analyses, including differences in days' supply and out-of-pocket costs between mail-order and local pharmacies. Although we cannot conclusively determine a causal relationship, the association between mail-order use and medication adherence deserves further investigation with a randomized study design.

Our findings reinforce the importance of system-level determinants of patient behavior. In response to a prevailing attitude of blaming the patient for poor adherence, the World Health Organization³⁰ has developed an adherence model that considers health system and socioeconomic factors, as well as patient-specific and medication-specific factors. Recent qualitative studies^{31,32} found that physicians rarely address system-level barriers to medication acquisition when prescribing a new medication. Physicians, nurses, or clinic-based support staff may be able to improve adherence when a new medication is prescribed by ensuring that patients who have efficient access to a reliable mail-order pharmacy system consider using it to obtain their refills.

Our findings also suggest the intriguing potential of larger organization-level interventions to improve adherence by promoting increased mail-order use. Recent review articles^{2,33} examining adherence intervention research take a despairing tone, noting that the field is "stuck," without good options to move forward. Although there have been more than 50 randomized controlled trials of adherence interventions for chronic medications, none have evaluated efforts to minimize system-related barriers to medication acquisition.^{34,35} Several studies³⁶⁻³⁸ focused on intensive efforts by pharmacists to provide ongoing medication counseling and demonstrated improved adherence and better outcomes. However, such approaches are costly and typically are not compensated by third-party payers. In current clinical settings, counseling at the time of medication refills is uncommon.^{39,40} Although proven effective, adoption of intensive counseling protocols may require a major expansion of professional responsibilities and represent a significant additional expense for health plans or employers.

■ **Table 2.** Adjusted Predicted Percentages of Mail-Order Pharmacy Use for a Newly Initiated Medication

Variable	Adjusted Predicted % ^a	P
Sex		
Male [Reference]	15.1	—
Female	14.7	.43
Age, y		
<65 [Reference]	15.4	—
≥65	14.3	.29
Race/ethnicity		
White, non-Latino [Reference]	24.1	—
African American	4.0	<.001
Latino	5.2	<.001
Asian/Pacific Islander	8.4	<.001
Native American	9.5	.004
Mixed race/ethnicity	8.0	<.001
Missing race/ethnicity	7.6	<.001
Comorbidities		
0-1 [Reference]	15.2	—
>1	14.0	.12
Smoker		
No [Reference]	15.2	—
Yes	12.2	.01
Socioeconomic deprivation score quartile		
1, Least deprived [Reference]	20.5	—
2	12.1	<.001
3	10.8	<.001
4, Most deprived	8.4	<.001
Insurance type		
Commercial non-Medicare [Reference]	16.1	—
Medicare Part D group	15.0	.93
Medicare Part D individual	10.5	<.001
Use of antidepressant		
No [Reference]	14.8	—
Yes	15.4	.44
Use of insulin		
No [Reference]	15.6	—
Yes	12.2	<.001
Index medication		
Generic [Reference]	14.1	—
Brand name	18.1	<.001
Use of nonformulary medication		
No [Reference]	15.0	—
Yes	13.1	.12
Financial incentive to order by mail		
No [Reference]	10.1	—
Yes	35.3	<.001
Distance from home to the local pharmacy, mean, miles		
<4 [Reference]	13.3	—
≥4	16.5	<.001

^aHolding all other covariates at their mean value. Adjusted for age; sex; race/ethnicity; socioeconomic deprivation score; number of comorbidities; smoking status; use of any nonformulary medication, antidepressant, or insulin; insurance type; financial incentive to order by mail; length of therapy with the index medication; and whether the index medication was generic or brand name.

■ **Table 3.** Adjusted Predicted Percentages of Good Medication Adherence by Pharmacy Type

Medication Class	Adjusted Predicted % (95% Confidence Interval) ^a		Percentage Point Difference in Good Adherence ^b
	Mail-Order Pharmacy Users	Local Pharmacy Users	
Overall	84.7 (83.2-86.2)	76.9 (76.1-77.8)	7.8
Antiglycemic	81.8 (78.6-84.9)	75.2 (73.6-76.8)	6.6
Antihypertensive	88.1 (86.2-90.0)	80.4 (79.3-81.6)	7.7
Lipid lowering	81.7 (78.4-85.0)	72.4 (70.5-74.4)	9.3

^aAdjusted for age; sex; race/ethnicity; socioeconomic deprivation score; number of comorbidities; smoking status; use of any nonformulary medication, antidepressant, or insulin; insurance type; financial incentive to order by mail; length of therapy with the index medication; and whether the index medication was generic or brand name.
^bAll $P < .001$ for the difference in the predicted percentages between mail-order and local pharmacy users.

Developing effective strategies to increase mail-order pharmacy use could move the field of adherence intervention research in an important new direction. Our findings provide evidence supporting the development and evaluation of interventions to increase mail-order use. Although these interventions would not enhance existing levels of pharmacist counseling, they would potentially be appealing for several other reasons. Assuming similar generic dispensing rates across pharmacy type, mail-order pharmacies seem to be cost saving for a health system after the associated increase in medication use is taken into account.^{11,13} Many patients save money when ordering their medications by mail, and efforts to increase mail-order use among interested patients may be well accepted by patients and health systems. Interventions to increase mail-order use would, in many cases, take advantage of existing system infrastructure, further promoting sustainability. Many health systems, including the Department of Veterans Affairs,⁴¹ have well-established mail-order pharmacy systems that efficiently fill several million prescriptions per year.

Despite their potential benefits, interventions to increase mail-order pharmacy use would need to be carefully designed and implemented to avoid inadvertently harming patients. Such interventions should not come at the expense of face-to-face pharmacist time needed to clarify dosing schedules or check for adverse drug interactions, including dietary supplements or over-the-counter medications. Research studies that carefully assess the potential benefits and harms of increasing mail-order pharmacy use on a large scale are warranted.

Our study has several limitations. First, it was cross-sectional and cannot conclusively determine a causal relationship. Second, because of sample size limitations, we were unable to compare adherence among patients who use mail-order exclusively versus those who use local pharmacies exclusively. Third, we did not measure medication consumption, although our claims-based measure has been validated against pill counts.¹⁹ Fourth, the findings may not generalize

to fee-for-service settings with less integrated medication delivery systems or to patients who do not have diabetes. Fifth, we measured adherence to a single medication rather than multiple medications taken simultaneously. Sixth, we measured adherence only up to 15 months after the first medication fill, so our findings may not reflect long-term changes in adherence.

In summary, refilling a newly prescribed diabetes-related medication by mail is associated with a greater likelihood of good adherence compared with refilling at a local pharmacy. Minority patients and patients of low socioeconomic status have particularly low rates of mail-order pharmacy use. Although our findings should be confirmed in a randomized clinical trial, encouraging the use of existing efficient mail-order pharmacies may represent a novel, low-cost, and sustainable approach to improve medication adherence.

Author Affiliations: From the Division of General Internal Medicine, Department of Medicine, The David Geffen School of Medicine at UCLA (OKD), University of California, Los Angeles, CA; and the Division of Research (JAS, WTD, MMP, CSU, AJK), and the Pharmacy Outcomes Research Group (JC), Kaiser Permanente Northern California, Oakland, CA.

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Address correspondence to: O. Kenrik Duru, MD, MSHS, Division of General Internal Medicine, Department of Medicine, The David Geffen School of Medicine at UCLA, University of California, Los Angeles, 911 Broxton Plaza, Los Angeles, CA 90024. E-mail: kduru@mednet.ucla.edu.

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