Title

Potential Savings Associated with Drug Substitution in Medicare Part D: The Translating Research into Action for Diabetes (TRIAD) Study

Journal

Journal of General Internal Medicine, 29(1)

ISSN

0884-8734

Authors

Duru, O Kenrik
Ettner, Susan L
Turk, Norman
et al.

Publication Date

2014

DOI

10.1007/s11606-013-2546-6

Peer reviewed

Potential Savings Associated with Drug Substitution in Medicare Part D: The Translating Research into Action for Diabetes (TRIAD) Study

O. Kenrik Duru, MD[1], Susan L. Ettner, PhD[1,4], Norman Turk, MS[1], Carol M. Mangione, MD[1,4], Arleen F. Brown, MD, PhD[1], Jeffery Fu, PharmD[1], Leslie Simien, PharmD[1], and Chien-Wen Tseng, MD[2,3]

[1]David Geffen School of Medicine, University of California, Los Angeles, CA, USA; [2]John A. Burns School of Medicine, University of Hawaii, Honolulu, HI, USA; [3]Pacific Health Research and Education Institute, Honolulu, HI, USA; [4]Department of Health Policy and Management, UCLA Fielding School of Public Health, University of California, Los Angeles, Los Angeles, CA, USA.

BACKGROUND: Drug substitution is a promising approach to reducing medication costs.

OBJECTIVE: To calculate the potential savings in a Medicare Part D plan from generic or therapeutic substitution for commonly prescribed drugs.

DESIGN: Cross-sectional, simulation analysis.

PARTICIPANTS: Low-income subsidy (LIS) beneficiaries (n=145,056) and non low-income subsidy (non-LIS) beneficiaries (n=1,040,030) enrolled in a large, national Part D health insurer in 2007 and eligible for a possible substitution.

MEASUREMENTS: Using administrative data from 2007, we identified claims filled for brand-name drugs for which a direct generic substitute was available. We also identified the 50 highest cost drugs separately for LIS and non-LIS beneficiaries, and reached consensus on which drugs had possible therapeutic substitutes (27 for LIS, 30 for non-LIS). For each possible substitution, we used average daily costs of the original and substitute drugs to calculate the potential out-of-pocket savings, health plan savings, and when applicable, savings for the government/LIS subsidy.

RESULTS: Overall, 39 % of LIS beneficiaries and 51 % of non-LIS beneficiaries were eligible for a generic and/or therapeutic substitution. Generic substitutions resulted in an average annual savings of $160 in the case of LIS beneficiaries and $127 in the case of non-LIS beneficiaries. Therapeutic substitutions resulted in an average annual savings of $452 in the case of LIS beneficiaries and $389 in the case of non-LIS beneficiaries.

CONCLUSIONS: Our findings indicate that drug substitution, particularly therapeutic substitution, could result in significant cost savings. There is a need for additional studies evaluating the acceptability of therapeutic substitution interventions within Medicare Part D.

Received December 4, 2012
Revised June 4, 2013
Accepted June 18, 2013
Published online August 22, 2013

KEY WORDS: pharmacoeconomics; Medicare; health care policy.
J Gen Intern Med 29(1):230–6
DOI: 10.1007/s11606-013-2546-6

Medicare Part D provides drug coverage for almost 28 million enrollees.[1] Medicare Part D beneficiaries take five medications on average and fill more than 30 prescriptions each year. One in five beneficiaries has out-of-pocket drug costs exceeding $100 per month,[2] and 10 % use less medication than prescribed because of cost.[3] The most vulnerable low-income Medicare beneficiaries can qualify for significantly reduced out-of-pocket costs through the Part D low-income subsidy (LIS). However, the LIS program does not reduce the overall cost of medications, and much of the cost burden is transferred from individual beneficiaries to the government. Therefore, although the burden of rising out-of-pocket drug costs is likely to ease somewhat with the gradual elimination of the Part D coverage gap by 2020,[4] additional strategies to reduce drug costs, including out-of-pocket, health plan, and government subsidy costs, are still very much needed.

Much of the effort to reduce drug costs has been through "direct" generic substitution, i.e., replacing a brand-name drug with its less expensive generic equivalent, when available. This approach has been relatively successful, due to the loss of patent protection for several brand-name drugs, as well as the widespread use of tiered pricing strategies that encourage patients to select lower-cost generic drugs.[5–7] In 2006, generics were dispensed 88 % of the time when a direct generic substitution was available, and approximately 60 % of Medicare Part D prescriptions were for generic medications.[8,9] Given the already high use of generic drugs in Medicare Part D, it is unclear that direct generic substitution alone will produce further significant cost-savings.

Therapeutic substitution, defined as the use of a less expensive substitute that is not biologically equivalent but has a similar clinical/treatment effect as the original medica-

tion, is another option to limit the cost of prescription drugs. A cost analysis of potential anti-hypertensive therapeutic substitutions projected annual savings of up to $1.2 billion.[10] Studies estimate that the savings associated with routine therapeutic substitutions of one statin for another or one proton pump inhibitor (PPI) for another are substantial.[11–13] While almost 90 % of hospitals in the United States have implemented cost-saving therapeutic substitution policies for inpatients in order to align with inpatient formularies, this practice is less common in the outpatient setting.[14,15] However, some health plans have successfully implemented cost-saving therapeutic outpatient substitution policies for medications with similar mechanisms of action and side effect profiles (e.g., statins) with no change in clinical outcomes and no increase in medication-related adverse effects.[11,16] These studies precede the Medicare Part D Program and were focused on a single medication class.

In the current analyses, we used 2007 data from Medicare Part D Prescription Drug Plans (PDP) offered by a large, national health insurer to calculate the potential cost savings from possible generic or therapeutic substitutions for many commonly prescribed drugs. As our primary outcomes, we estimated the annual cost savings with each possible substitution, as well as the average cost savings to the beneficiary (out-of-pocket costs) and the health plan, for beneficiaries that did not enter the coverage gap in 2007. For beneficiaries enrolled in the LIS program, we also estimated the cost savings that would be applied to the government/LIS subsidy. As the exact cost savings in our models are specific to the health plan for which we have data and cannot be generalized, the intent of these analyses is not to emphasize precise dollar amounts, but rather to estimate the magnitude of potential savings in Medicare Part D plans that is possible with generic and/or therapeutic substitution.

METHODS

Data Source/Population

We analyzed pharmacy claims of Medicare Part D beneficiaries across the United States who were ≥ 65 years by January 1, 2006 and had complete pharmacy claims data (n=2,044,377). The Part D health plan is responsible for tracking drug costs in order to calculate the threshold for coverage gap entry. Therefore, they are provided with daily feeds on prescriptions from local pharmacies for which the beneficiary provides their Medicare identification card. This information is included in the claims files that we received.

We excluded beneficiaries who were not continuously enrolled in the plan for the duration of 2007 (n=194,142), exceeded the cost threshold for entry into the coverage gap (n=568,360), were institutionalized (n=79,944), or for whom we could not clarify LIS versus non-LIS status (n=16,845). We examined the prescription claims of the remaining sample of LIS beneficiaries (n=145,056) and non-LIS beneficiaries (n=1,040,030) for possible generic and therapeutic substitutions. This study was approved by the Institutional Review Board of the University of California, Los Angeles.

Pharmacy Claims

Health plan pharmacy claims indicated whether the drug was filled as a generic or brand-name, whether a direct generic equivalent was available for brand-name drugs, the date filled and days' supply provided. Cost information for both the original and substituted medications, including out-of-pocket costs, health plan costs, and where applicable, governmental subsidy costs, was also derived from pharmacy claims.

Generic Substitution Methods

Using Generic Product Indicator (GPI) data, we identified all claims filled for brand-name drugs for which there was a direct generic substitute available. For each brand-name drug (e.g. Prozac), we calculated the average daily cost (ADC) of its direct generic equivalent (out-of-pocket costs plus health plan costs) by taking all claims filled for the generic equivalent (e.g. fluoxetine), and averaging the cost per day of all the claims. Then, to calculate the potential annual cost savings, we identified all brand-name drug claims where the ADC of the brand-name drug was greater than the ADC of the generic equivalent, and then summed the savings across all claims. In situations where a generic drug became available midway during 2007, such as extended release metoprolol, the cost savings was calculated based on substituting the brand-name drug with its generic equivalent starting at the date of generic availability and continuing for the remainder of the calendar year.

Therapeutic Substitution Methods

Based on claims data, we identified separate lists of 50 medications that contributed the most to total drug expenditures in 2007 for LIS beneficiaries and for non-LIS beneficiaries, and six members of the study team (four primary care physicians with more than 10 years of clinical experience – OKD, CMM, CWT, AFB; and two pharmacists – JF, LS) determined whether a possible therapeutic substitution existed for each medication. We only included therapeutic substitutions that all six team members agreed were clinically appropriate. For 27 of the 50 medications on the LIS list and 30 of the 50 medications on the non-LIS list, we agreed on a possible therapeutic equivalent and the equipotent dose of substitutions to maintain clinical effectiveness. For example, we identified the 20 mg dose of simvastatin as a possible substitution for the 10 mg dose of atorvastatin, and the 40 mg dose of rosuvastatin as a possible substitution for the 80 mg

dose of atorvastatin. For the remaining medications, we agreed that no therapeutic substitution was possible. For each of the potential substitutions, we calculated potential cost savings by taking the difference between the ADC of each drug and the ADC of its therapeutic substitute and summing these differences across all claims filled for each of the drugs. We only made therapeutic substitutions that were cost saving for both the patient and the plan (and the government subsidy in the case of LIS beneficiaries), and did not include pill-splitting in our substitution algorithm.

Statistical Analysis

For each possible substitution, we calculated the potential annual cost savings, including out-of-pocket savings for the beneficiary, savings to the health plan, and savings for the government/LIS subsidy. As the substitutions we made would be inappropriate in some cases (e.g., prior unsuccessful attempt to start the substituted medication, specific patient-level indications necessitating use of a particular drug), calculating a total dollar amount would overestimate the actual cost savings that could be achieved by substitution. Therefore, we expressed the projected savings associated with substitution in dollars per-person, individually for each possible substitution. This allows the reader to assess the total population savings under any assumption about the percent of patients using a particular drug who would be appropriate for substitution.

RESULTS

Overall, 56,788 (39 %) of the LIS beneficiaries and 535,195 (51 %) of the non-LIS beneficiaries had a possible generic and/or therapeutic substitution. Importantly, among LIS beneficiaries, those with a possible substitution had a higher mean prescription count in 2007 (34 vs. 27, $p<0.001$) and accrued higher average per-person prescription costs, including health plan costs ($876 vs. $529, $p<0.001$), out-of-pocket costs ($114 vs. $81, $p<0.001$), and government subsidy costs ($454 vs. $307, $p<0.001$, Table 1), compared to beneficiaries without a possible substitution. Similar patterns were seen among non-LIS beneficiaries, although mean prescription counts were somewhat lower for both patients with and without a possible substitution (29 vs. 21, $p<0.001$) as compared to LIS beneficiaries. Non-LIS beneficiaries with a possible substitution accrued higher average per-person prescription costs, including health plan costs ($867 vs. $488, $p<0.001$) and out-of-pocket costs ($520 vs. $324, $p<0.001$), compared to beneficiaries without a possible substitution.

Among the subset of beneficiaries for whom a substitution was possible, 7,757 (14 %) of the LIS beneficiaries and 46,418 (9 %) of the non-LIS beneficiaries were eligible for one or more generic substitutions, while 52,143 (92 %) of the LIS beneficiaries and 511,752 (96 %) of the non-LIS beneficiaries were eligible for one or more therapeutic substitutions (Table 2). We estimated that generic substitutions resulted in an average annual savings in 2007 of $160 in the case of LIS beneficiaries and $127 in the case of non-LIS beneficiaries. For LIS beneficiaries, this includes average out-of-pocket savings of $14 and average savings for the government/LIS subsidy of $156. For non-LIS beneficiaries, this includes average out-of-pocket savings of $138. However, generic substitutions would result in an average cost increase to the health plan of $11 in the case of both LIS and non-LIS beneficiaries (Table 2).

Therapeutic substitutions resulted in an average annual savings in 2007 of $452 in the case of LIS beneficiaries and $389 in the case of non-LIS beneficiaries (Table 2). For LIS beneficiaries, this includes average out-of-pocket savings for LIS beneficiaries of $22 and average savings for the government/LIS subsidy of $126. For non-LIS beneficiaries, this includes average out-of-pocket savings of $113. The health plan would save an average of $305 in the case of LIS beneficiaries and $276 in the case of non-LIS beneficiaries.

Table 3 shows information on cost savings for each of the generic and therapeutic substitutions for LIS beneficiaries. The most common potential substitutions were for PPIs ($n=15,961$) and statins ($n=13,989$). The cost savings associated with substituting generic omeprazole for brand-name PPIs including Protonix, Nexium, and Prevacid in 2006 were substantial, including an average annual savings among the group in whom a substitution could have been made of $467, with health plan per-person savings of $358, out-of-pocket savings of $18 per person, and government/LIS subsidy savings of $91 per person (Table 3). The potential savings for therapeutic statin substitutions were similar. In addition, there were an additional seven substitutions that would have resulted in over $150 of per-person savings for the health plan, and an additional six substitutions that would have resulted in over $100 of per-person savings for the government/LIS subsidy. For non-LIS beneficiaries, potential substitutions in 2007for several different medication classes would have also resulted in substantial per-person health plan savings as well as per-person out-of-pocket savings (Table 4). A large percentage of the potential substitutions were for statin medications ($n=245,566$), with a three-fold greater number of eligible patients than for any other specific substitution.

DISCUSSION

Using 2007 data from a large Medicare Part D provider, our data indicate that possible therapeutic drug substitutions

Table 1. Baseline Characteristics, by LIS Status and Eligibility for a Generic or Therapeutic Substitution

	LIS beneficiaries			Non-LIS beneficiaries		
	Eligible for substitution (*n*=56,788)	NOT eligible for substitution (*n*=88,268)	P value	Eligible for substitution (*n*=535,195)	NOT eligible for substitution (*n*=504,835)	P value
Age (SD)	75.8 (7.5)	75.7 (7.7)	0.87	75.2 (7.3)	74.9 (7.4)	< 0.001
Female (%)	72.1	72.8	.007	61.0	64.3	< 0.001
Receiving Medicaid (%)	15.5	15.6	0.48	–	–	–
Mean per-person prescription count in 2007 (SD)	34.2 (19.4)	27.0 (20.5)	< 0.001	28.9 (17.2)	20.6 (16.4)	< 0.001
Percentage of all prescriptions that were generic (%)	59.1	71.5	< 0.001	58.8	69.7	< 0.001
Mean overall per-person prescription cost in 2007 (SD) (calculated as the sum of costs for the health plan, patient, and government subsidy)	$1,444 (599)	$916 (682)	< 0.001	$1,386 (604)	$812 (650)	< 0.001
Health plan	$876 (425)	$529 (458)	< 0.001	$867 (434)	$488 (458)	< 0.001
Patient	$114 (87)	$81 (86)	< 0.001	$520 (266)	$324 (271)	< 0.001
Government subsidy	$454 (260)	$307 (271)	< 0.001	–	–	–

would result in two to three times greater annual cost savings than possible generic substitutions, in both LIS and non-LIS populations. There would be notable savings for the government with a decrease in payments for the low-income subsidy for both generic and therapeutic substitution. If these possible therapeutic substitutions were made for even a subset of eligible beneficiaries, there would also be substantial savings for health plans and individuals. While drug costs differ across health systems and vary over time, these findings indicate the importance of examining generic and therapeutic substitutions as a next step to lowering drug costs within Medicare. Since Medicare is unable to negotiate volume purchasing discounts for medications, these substitution approaches represent an alternative cost-control strategy.

Acknowledging that exact savings would differ across various health plans, if 75 % of eligible non-LIS Medicare Part D patients within our sample substituted generic omeprazole for brand-name PPIs, the approximate savings would be $21.7 million for the health plan and $6.0 million in out-of-pocket costs for beneficiaries. If 75 % of LIS beneficiaries in this health plan substituted generic omeprazole for brand-name PPIs, the approximate savings to the government would be $1.1 million in lower LIS subsidies.

Our calculated estimates of cost savings are comparable to one "real-world" statin substitution program described in the literature, which reported an annual per-person savings of $317 in 2002 (equivalent to $363 in 2007 when inflation-adjusted).[17] A second study of statin substitutions reported a total annual per-person savings in 2007 of over $1,100, more than twice our estimate.[18] However, this program, which substituted simvastatin for atorvastatin for both commercial and Medicare patients, was located in Michigan where the monthly cost of simvastatin was capped at $10 in 2007,[18] which is lower than the corresponding cost of simvastatin in our data set.

For our analysis, we decided on potential therapeutic substitutions based on the clinical judgment of four primary care providers with active clinical practices that include older adults, and two practicing pharmacists. We did not make therapeutic substitutions in which we felt that one medication had significantly greater efficacy than another, or when a medication posed a significantly increased risk of patient harm. In real-world settings, the use of therapeutic substitution will require buy-in from both Medicare providers and beneficiaries, and will necessitate consideration

Table 2. Estimated Per-Person Cost Savings with Generic or Therapeutic Substitution

Generic substitution	LIS beneficiaries (*n*=7,757)	Non-LIS beneficiaries (*n*=46,418)
Annual savings (sum of savings for health plans, patients, and government subsidy)	$160 (241)	$127 (213)
Savings for the health plan	− $11 (134)	− $11 (112)
Savings for the patient	$14 (33)	$138 (184)
Savings for the government subsidy	$156 (188)	–
Therapeutic substitution	LIS beneficiaries (*n*=52,143)	Non-LIS beneficiaries (*n*=511,752)
Annual savings (sum of savings for health plans, patients, and government subsidy)	$452 (360)	$389 (344)
Savings for the health plan	$305 (269)	$276 (251)
Savings for the patient	$22 (31)	$113 (120)
Savings for the government subsidy	$126 (115)	–

Table 3. Estimated Cost Savings of Generic and Therapeutic Substitutions in 2007 for LIS Beneficiaries, by Medication

Prescribed medication/s	Substituted medication	Number of Part D beneficiaries with viable substitutions	Estimated annual savings (plan+out-of-pocket+gov't subsidy)	Estimated plan savings (per-person)	Estimated out-of-pocket savings (per-person)	Estimated savings to the government subsidy (per-person)
Protonix, Nexium, Prevacid, Aciphex	Omeprazole	15,961	$467.33	$357.62	$18.34	$91.37
Lipitor, Crestor, Vytorin,	Simvastatin/Crestor	13,989	$491.12	$339.96	$23.46	$127.70
Norvasc, Nifedipine	Amlodipine	6,286	$112.95	$57.17	$8.09	$47.70
Celebrex	Ibuprofen	4,436	$381.11	$157.99	$14.51	$208.60
Toprol XL, Coreg	Metoprolol ER	3,989	$347.25	$220.18	$19.84	$107.22
Flomax	Doxazosin	3,696	$362.11	$237.65	$19.70	$104.77
Lexapro	Citalopram	3,177	$339.23	$221.66	$19.84	$97.72
Ambien	Zolpidem	2,930	$274.58	$211.19	$11.82	$51.57
Lexxel/Lotrel	Amlodipine+Lisinopril	2,782	$200.30	$123.74	$14.96	$61.61
Altace	Lisinopril	2,403	$353.48	$183.56	$24.99	$144.93
Detrol	Oxybutynin	2,161	$283.61	$193.46	$14.60	$75.55
Caduet	Amlodipine+Dose-Dependent Statin	440	$420.01	$130.41	$26.15	$263.45
Actonel	Fosamax	176	$41.95	$31.81	$3.16	$6.98
Diltiazem/Cartia/Taztia	Verapamil	150	$42.76	$35.00	$2.15	$5.61
Diovan, Cozaar	Benicar	130	$247.25	$80.19	$10.06	$157.00
Aricept	Namenda	49	$45.47	$27.19	$4.53	$13.74
Diovan HCT, Hyzaar, Benicar HCT	Benicar+HCTZ	36	$148.03	$62.31	$23.04	$62.68

of factors other than cost, such as potential differences in medication-related side effects or heterogeneity in patient responses to different medications within the same class. Ultimately, both physicians and patients will require all necessary clinical information and drug costs to make informed decisions about any various tradeoffs associated with that substitution.

The acceptability of a given substitution for a particular patient depends on differences in specific comorbidities that alter patient risk, or willingness to tolerate medication-related side effects. As an example of slight medication differences, the substitution of long acting metoprolol for carvedilol will be appropriate for the majority of patients with congestive heart failure. However, carvedilol has a somewhat increased vasodilatory effect and results in slightly lower blood pressure as compared to metoprolol, and some patients and providers may choose to preferentially use carvedilol for that reason.

Of note, generic substitution could potentially reduce out-of-pocket costs for a proportion of the members in our sample, and this cost-saving strategy should therefore still be pursued. We found that possible new generic substitutions actually result in a slight average cost increase for the health plan, because in many cases the plan does not

Table 4. Estimated Cost Savings of Generic and Therapeutic Substitutions in 2007 for non-LIS Beneficiaries, by Medication

Prescribed medication/s	Substituted medication	Number of Part D beneficiaries with viable substitutions	Estimated annual savings (plan+out-of-pocket)	Estimated plan savings (per-person)	Estimated out-of-pocket savings (per-person)
Lipitor, Crestor, Vytorin, Lovastatin, Pravastatin	Simvastatin/Lovastatin/ Crestor	245,566	$330.60	$245.52	$85.08
Protonix, Nexium, Prevacid	Omeprazole	80,670	$456.39	$357.91	$98.47
Norvasc, Nifedipine	Amlodipine	41,492	$125.63	$73.82	$51.81
Diltiazem/Cartia/Taztia	Verapamil	39,660	$136.03	$133.22	$2.81
Flomax	Doxazosin	38,203	$421.50	$277.90	$143.59
Diovan, Cozaar	Benicar	33,635	$98.17	$84.84	$13.33
Celebrex	Ibuprofen	25,275	$345.32	$144.46	$200.87
Toprol XL, Coreg	Metoprolol ER	24,801	$356.96	$231.97	$124.99
Actonel, Boniva	Fosamax	23,638	$30.14	$22.94	$7.21
Lexapro	Citalopram	23,513	$352.21	$230.19	$122.02
Altace	Lisinopril	22,130	$377.51	$194.87	$182.63
Lexxel/Lotrel	Amlodipine+Lisinopril	17,439	$209.01	$126.26	$82.75
Detrol	Oxybutynin	16,339	$339.30	$225.38	$113.93
Ambien	Zolpidem	12,437	$259.51	$200.12	$59.39
Antara/Tricor/Triglide	Fenofibrate	11,398	$313.25	$170.65	$142.61
Aricept	Namenda	695	$72.22	$56.67	$15.55
Avodart	Finasteride	549	$88.10	$25.12	$62.97
Levothroid/Synthroid	Levothyroxine	503	$97.32	$25.18	$72.14
Diovan HCT, Benicar HCT	Benicar+HCTZ	288	$65.08	$49.94	$15.14

cover the generic substitutes. The great majority of generic substitutions that result in cost savings for the plan may have already been instituted. There appears to be little financial incentive for health plans to make additional generic substitutions that are currently available, despite the potential savings they would create for beneficiaries. However, as generic equivalents for existing popular brand-name medications become available, health plans are likely to institute those new generic substitutions.

We chose to exclude pill splitting from our substitution algorithm because of the variation by manufacturer in whether the substituted pills are scored and in the size of each pill, which determine how easily these medications can be split by patients. Furthermore, instructions on how to split pills may be confusing for some patients and lead to errors in splitting and incorrect dosage regimens.[19] However, multiple trials comparing equipotent split and intact anti-hypertensive, statin, and psychotropic pills have failed to show any difference in clinical outcomes between the groups.[20–22] Pill splitting of selected medications may represent another systematic approach to achieve additional cost savings within Medicare.

Our study has several limitations. First, we were unable to clearly define subgroups for which a particular substitution may have been relatively contraindicated (e.g., substituting naprosyn for celecoxib in a patient at high risk for upper gastrointestinal bleeding), or who may have tried and failed less expensive drugs. Our estimates of the number of potentially eligible people should therefore be interpreted as an upper bound on the actual population appropriate for each substitution. Second, we did not have information on drug discounts offered by manufacturers to health plans, so our results may overestimate the savings for health plans for drug substitutions. Finally, the cost savings associated with drug substitutions may be slightly offset by the increased cost of physician visits to switch the medications and/or monitor post-switch clinical status. Unlike the drug savings, however, any increases in associated medical costs should be time-limited and perhaps offset by long-term savings due to improved drug adherence and reduced use of high-cost healthcare services, such as hospitalizations and emergency department visits.

In summary, results of our simulation analyses within a Medicare Part D sample indicate that therapeutic substitution will result in greater cost savings when compared with generic substitution. However, therapeutic substitution programs will need to be carefully planned, relying on physician input regarding the overall acceptability of appropriate equipotent substitutions, as well as identifying which patients are not candidates for medication substitution. There is a need for well-designed studies evaluating real-world therapeutic substitution interventions in Medicare Part D that track utilization and costs as well as clinical outcomes. Such interventions may include providing physicians with cost information for potential medication substitutes; most physicians do not currently have easy access to that information during patient visits.[23] These types of interventions will be particularly important in controlling medication costs over the next decade, as patients may have less incentive to limit their use of expensive brand-name drugs as the coverage gap is eliminated under health care reform.

Acknowledgements:
Contributors: *Significant contributions to this study were made by members of the Translating Research into Action for Diabetes (TRIAD) Study Group.*

Funders: *This study was jointly funded by Program Announcement number 04005 from the Centers for Disease Control and Prevention (Division of Diabetes Translation) and the National Institute of Diabetes and Digestive and Kidney Diseases. Drs. Mangione and Duru are supported in part by the UCLA Resource Center for Minority Aging Research, Center for Health Improvement of Minority Elderly (RCMAR/CHIME) under NIH/NIA Grant P30-AG021684. Dr. Mangione also received support from the NIH/NCATS UCLA CTSI Grant Number UL1TR000124. Dr. Duru also received support from the Amos Medical Faculty Development Award from the Robert Wood Johnson Foundation as well as NIA Grant K08-AG033630.*

Prior Presentations: *A prior version of these analyses was presented at the 33rd Annual Meeting of the Society of General Internal Medicine in Minneapolis MN, April 28 - May 1, 2010.*

Conflicts of Interest: *The authors declare that they do not have any conflicts of interest.*

Corresponding Author: *O. Kenrik Duru, MD; Division of General Internal Medicine, David Geffen School of Medicine, University of California, Los Angeles, 911 Broxton Plaza, Los Angeles, CA 90095, USA (e-mail: kduru@mednet.ucla.edu).*

REFERENCES

1. The Henry J. Kaiser Family Foundation. Medicare Chartbook, Fourth Edition, 2010. Menlo Park, CA: Kaiser Family Foundation. Available at: www.kff.org/medicare/upload/8103.pdf. Accessed December 4, 2012.
2. The Henry J. Kaiser Family Foundation. Retail prescription drugs filled at pharmacies (Annual per capita by age), 2009. Menlo Park, CA: Kaiser Family Foundation. Available at: http://www.statehealthfacts.org/comparetable.jsp?ind=268&cat=5. Accessed December 4, 2012.
3. **Madden JM, Graves AJ, Ross-Degnan D, Briesacher BA, Soumerai SB.** Cost-related medication nonadherence after implementation of Medicare Part D, 2006–2007. JAMA. 2009;302:1755–6.
4. The Henry J. Kaiser Family Foundation. Explaining health care reform: key changes to the Medicare Part D drug benefit coverage gap, 2010. Menlo Park, CA: Kaiser Family Foundation. Available at: http://www.kff.org/healthreform/upload/8059.pdf. Accessed December 4, 2012.
5. **Aitken M, Berndt ER, Cutler DM.** Prescription drug spending trends in the United States: looking beyond the turning point. Health Aff (Millwood). 2009;28:w151–60.
6. **Gilman BH, Kautter J.** Impact of multitiered copayments on the use and cost of prescription drugs among Medicare beneficiaries. Health Serv Res. 2008;43:478–95.
7. **Hartman M, Martin A, Nuccio O, Catlin A.** Health spending growth at a historic low in 2008. Health Aff (Millwood). 2010;29:147–55.
8. **Zhang JX, Yin W, Sun SX, Alexander GC.** The impact of the Medicare Part D prescription benefit on generic drug use. J Gen Intern Med. 2008;23:1673–8.
9. **Levinson DR.** Generic drug utilization in the Medicare Part D program. Washington, DC: Department of Health and Human Services, OEI-05-07-00130, 2007. Available at: https://oig.hhs.gov/oei/reports/oei-05-07-00130.pdf. Accessed December 4, 2012.

10. **Fischer MA, Avorn J.** Economic implications of evidence-based prescribing for hypertension: can better care cost less? JAMA. 2004;291:1850–6.
11. **Schneeweiss S, Maclure M, Dormuth CR, Glynn RJ, Canning C, Avorn J.** A therapeutic substitution policy for proton pump inhibitors: clinical and economic consequences. Clin Pharmacol Ther. 2006;79:379–88.
12. **Moon JC, Bogle RG.** Switching statins. BMJ. 2006;332:1344–5.
13. **Gumbs PD, Verschuren WM, Souverein PC, et al.** Society already achieves economic benefits from generic substitution but fails to do the same for therapeutic substitution. Br J Clin Pharmacol. 2007;64:680–5.
14. American Society of Health-System Pharmacists. ASHP guidelines on medication cost management strategies for hospitals and health systems. Am J Health Syst Pharm. 2008;65:1368–84.
15. American College of Clinical Pharmacy. ACCP position statement: guidelines for therapeutic interchange. Pharmacotherapy. 2005;25:1666–80.
16. **Cheetham TC, Chan J, Benson V, Richmond C, Levin E, Campen D.** Successful conversion of patients with hypercholesterolemia from a brand name to a generic cholesterol-lowering drug. Am J Manag Care. 2005;11:546–52.
17. **Billups SJ, Plushner SL, Olson KL, Koehler TJ, Kerzee J.** Clinical and economic outcomes of conversion of simvastatin to lovastatin in a group-model health maintenance organization. J Manag Care Pharm. 2005;11:681–6.
18. **Sy FZ, Choe HM, Kennedy DM, et al.** Moving from A to Z: successful implementation of a statin switch program by a large physician group. Am J Manag Care. 2009;15:233–40.
19. **Freeman MK, White W, Iranikhah M.** Tablet splitting: a review of weight and content uniformity. Consult Pharm. 2012;27:341–52.
20. **Freeman MK, White W, Iranikhah M.** Tablet splitting: a review of the clinical and economic outcomes and patient acceptance. Second of a 2-part series. Consult Pharm. 2012;27:421–30.
21. **Gee M, Hasson NK, Hahn T, Ryono R.** Effects of a tablet-splitting program in patients taking HMG-CoA reductase inhibitors: Analysis of clinical effects, patient satisfaction, compliance, and cost avoidance. J Manag Care Pharm. 2002;8:453–8.
22. **Weissman EM, Dellenbaugh C.** Impact of splitting risperidone tablets on medication adherence and on clinical outcomes for patients with schizophrenia. Psychiatr Serv. 2007;58:201–6.
23. **Tseng CW, Buenconsejo-Lum L, Manlucu L, Hixon A.** Physicians' willingness and barriers to considering cost when prescribing. Hawaii Med J. 2006;65(318):320–1.