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# ASSOCIATIONS BETWEEN PROVIDER SPECIALTY AND USE OF FOLLOW-UP TESTING AMONG PATIENTS ON PREVENTIVE PHARMACOLOGICAL THERAPY FOR URINARY STONE DISEASE

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## Abstract

**Purpose:** The American Urological Association (AUA) Medical Management of Kidney Stones guideline outlines recommendations on follow-up testing for patients prescribed preventive pharmacological therapy (PPT). We evaluated adherence to these recommendations by provider specialty.

**Methods:** Using claims data from working-age adults with urinary stone disease (2008–2019), we identified patients prescribed a PPT agent (a thiazide diuretic, alkali citrate therapy, allopurinol, or a combination thereof) and the specialty of the prescribing physician (urology, nephrology, and general practice). Next, we identified patients who completed a 24-hour urine collection prior to their prescription fill. We then measured adherence to 3 recommendations outlined in the AUA guideline. Finally, we fit multivariable logistic regression models evaluating associations between prescribing provider specialty and adherence to recommended follow-up testing.

**Results:** Among 2600 patients meeting study criteria, 1523 (59%) adhered to ≥1 follow-up testing recommendation, with a significant increase over the study period. Nephrologists had

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higher odds of adherence to ≥1 follow-up test compared to urologists (odds ratio, 1.52; 95% confidence interval, 1.19 to 1.94; $P<0.01$). Significant differences in adherence to the 3 individual guideline recommendations were also observed by specialty.

**Conclusion:** Following initiation of PPT, adherence to guideline-recommended follow-up testing was low overall. There exist meaningful specialty-specific differences in the use of this testing.

### Keywords

urolithiasis; metabolic evaluation; tertiary prevention; follow-up testing

## INTRODUCTION

Given that ≥50% of adults who experience a stone-related event will have a recurrence within 10 years,[1] urinary stone disease (USD) is best viewed as a chronic condition marked by acute exacerbations for which tertiary prevention can play an important management role. To reduce the recurrence risk, contemporary practice guidelines recommend consideration of a thiazide diuretic, potassium citrate, or allopurinol—collectively referred to as preventive pharmacological therapy (PPT)—for patients with USD.[2] Further, these guidelines recommend on-treatment follow-up testing for monitoring response to and tailoring of PPT.[3]

Yet, despite recommendations for repeat 24-hour urine collections and periodic blood testing after initiation of PPT, there are reasons to believe that adherence to them is low.[3] Namely, a systematic review commissioned by the Agency for Healthcare Research and Quality found no randomized controlled trial or observational data examining the utility of post-baseline urine and blood chemistry measurement in reducing stone recurrence.[4] Absent these supportive data, providers may opt not to perform it. Indeed, prior studies show that fewer than 1 in 5 patients with abnormalities on initial 24-hour urine collection complete a repeat collection within 6 months of their first.[5,6] Further, urologists obtained a repeat 24-hour urine collection less frequently after an initial abnormal finding than other providers who manage patients with USD,[6] suggesting that use of follow-up testing may vary by specialty.

To better understand the use of guideline-recommended on-treatment follow-up testing, we analyzed medical claims data from working-age adults. We identified a cohort of patients with a physician-coded diagnosis of USD who were prescribed PPT by a urologist, nephrologist, or general practitioner. We distinguished the subset who completed a 24-hour urine collection prior to their first prescription fill. We then measured rates of guideline-recommended follow-up testing, including completion of subsequent 24-hour urine collection and therapy-specific serum studies. Finally, we evaluated associations between provider specialty and completion of this testing.

## METHODS

### Data source and study population

For this study, we analyzed data from Optum's de-identified Clinformatics® Data Mart Database, which includes deidentified inpatient, outpatient, and pharmacy claims from over

83 million commercially insured children and adults. Supplementary Figure 1 shows the steps that we followed in our cohort creation. Through previously described methods,[7] we identified all patients in the database aged 18 to 64 years with ≥2 submitted claims for USD or ≥1 stone-specific surgery between January 1, 2008, and December 31, 2019. To determine the latter, we used the *International Classification of Diseases* (ICD) and *Current Procedural Terminology* (CPT) codes listed in Supplementary Table 1. With appropriate National Drug Codes (Supplementary Table 2), we distinguished patients with a prescription fill for PPT (i.e., a thiazide diuretic, alkali citrate therapy, uric acid reducing agent, or a combination thereof) following completion of a 24-hour urine collection and within the 12 months that followed their index USD claim. We assessed 24-hour urine testing using the CPT code for 24-hour urinary oxalate (83945), which is highly specific for the metabolic evaluation of USD.[8]

We excluded patients without continuous insurance coverage and enrollment in a drug benefit plan for ≥12 months before their index USD claim and 18 months after their initial PPT prescription fill to ensure appropriate comorbidity adjustment and adequate follow-up, respectively. Additionally, we excluded patients enrolled in Medicare Advantage at any point between 12 months before their index USD claim and 18 months after their initial PPT prescription, as their healthcare utilization is incompletely captured in the database. We also excluded patients who were prescribed PPT agents within the 6 months preceding their index USD claim because these medications may have been prescribed for indications other than USD prevention. Finally, we excluded patients who received their first PPT prescription from providers other than a urologist, nephrologist, or general practitioner (provider category codes displayed in Supplementary Table 3). These 3 specialties wrote the majority of PPT prescriptions.

### Measuring use of on-treatment follow-up testing

We used the American Urological Association's Medical Management of Kidney Stones guideline first published in 2014 and confirmed in 2019 to determine whether patients with USD and prescribed PPT received follow-up care consistent with 3 recommendations: 1) "Clinicians should obtain a single 24-hour urine specimen for stone risk factors within 6 months of the initiation of treatment to assess response to dietary and/or medical therapy" (Guideline Statement 22); 2) "After the initial follow-up, clinicians should obtain a single 24-hour urine specimen annually or with greater frequency, depending on stone activity, to assess patient adherence and metabolic response" (Guideline Statement 23); and 3) "Clinicians should obtain periodic blood testing to assess for adverse effects in patients on pharmacological therapy" (Guideline Statement 24).[3] We created claims-based definitions corresponding to these 3 recommendations. The prescribing provider was not required to be the ordering provider for the follow-up testing. Note that, in order to be compliant with Guideline Statement 23, the patient had to have completed an initial follow-up 24-hour urine within 6 months of PPT initiation, followed by ≥1 subsequent 24-hour urine within a year of the aforementioned initial follow-up collection. Supplementary Table 4 displays the CPT codes that we used for PPT agent-specific serum tests. In order to be compliant with Guideline Statement 24, the patient had to have completed therapy-specific serum testing at least once within 6 months of initiating therapy.

### Statistical analysis

We performed descriptive statistics, including frequencies for categorical variables and means for continuous variables. We report sociodemographic characteristics of the cohort including age, sex, race/ethnicity, education, and region of residence. We also report clinical characteristics including the level of comorbid illness based on the Charlson Comorbidity Index,[9] high-risk status based on concurrent diagnoses known to increase stone recurrence risk (Supplementary Table 5), medication adherence defined as ≥80% days covered from the index PPT prescription fill to 3 months (percentage of days covered is the number of days available or "covered" by a certain medication divided by the total number of days in the follow-up period, multiplied by 100),[10] and PPT prescribed. Specifically, we report PPT prescribed in mutually exclusive categories (i.e., thiazide, alkali citrate, or uric acid reducing agent monotherapy or combination therapy).

We used bivariable statistics (chi-square tests for categorical variables and one-way ANOVA for continuous variables) to examine crude differences in patient sociodemographic and clinical characteristics by prescribing provider specialty. Next, we calculated overall adherence to follow-up testing recommendations by calendar year and evaluated temporal trends in adherence with the Cochran-Armitage trend test. We then fit multivariable logistic regression models to evaluate the association between prescribing provider specialty and adherence to guideline-recommended follow-up testing. From our multivariable models, we determined the predicted probability of adherence to individual on-treatment follow-up testing recommendations by provider specialty. The predicted rates are based on predicted population marginal means at each category for the variable of interest (i.e., provider specialty) derived from the multivariable logistic regression models, and then converted from the log-odds scale to percentages via an inverse logit transformation. Finally, we performed a sensitivity analysis, repeating the aforementioned analyses using a more flexible cutoff of 8 months, rather than 6 months, for the repeat 24-hour urine collection.

We conducted all statistical analyses using SAS Version 9.4 (SAS Institute, Inc., Cary, NC, USA). All of our statistical tests were 2-sided with the type I error rate set to 0.05. The Institutional Review Board at the University of Michigan Medical School determined that this study was exempt from its oversight.

## RESULTS

In total, 2600 adult patients met study inclusion criteria. Among them, urologists, nephrologists, and general practitioners were responsible for 74%, 15%, and 11% of PPT prescriptions, respectively. Fifty-nine percent ($n$=1523) of patients received care concordant with ≥1 guideline recommendation for on-treatment follow-up testing. Figure 1 highlights a significant increase in adherence to ≥1 follow-up testing recommendation over time: 53% in 2008, peaking at 68% in 2016, and decreasing to 62% in 2018 ($P$<0.01 for the temporal trend). This appeared to be driven by an increase in therapy-specific serum testing (increase from 43% in 2008 to 51% in 2018, $P$<0.01 for the temporal trend). However, adherence to ≥2 and all 3 follow-up recommendations did not change significantly over time ($P$=0.64 and $P$=0.27, respectively); neither did adherence to the repeat 24-hour urine within 6 months nor the subsequent 24-hour urine within 12 months ($P$=0.49 and $P$=0.29, respectively).

As shown in Table 1, there were significant bivariable differences between patients managed by urologists, nephrologists, and general practitioners with regards to age ($P$<0.01), sex ($P$<0.01), education ($P$=0.03), region of residence ($P$<0.01), level of comorbid illness ($P$=0.02), high-risk status ($P$<0.01), medication adherence ($P$<0.01), and therapy prescribed ($P$<0.01). Specifically, patients treated by urologists were more often male, had lower levels of education, and had lower levels of comorbid illness than those treated by nephrologists and general practitioners. They were also more likely to receive alkali citrate monotherapy and less likely to adhere to their medication. On the other hand, nephrologists cared for a high proportion of patients with concurrent diagnoses that put them at risk of stone recurrence, and general practitioners cared for older patients.

There were also significant bivariable differneces in adherence to ≥1, ≥2 and all 3 follow-up testing recommendations across specialties ($P$<0.01 for each comparison; Table 1). Crude rates of adherence to ≥1 recommended on-treatment follow-up test were lowest among patients treated by urologists, whereas adherence to ≥2 and all 3 recommended on-treatment follow-up tests were lowest among general practitioners. On multivariable analysis (Table 2), compared to patients who were managed by a urologist, those treated by a nephrologist had 52% higher odds of receiving ≥1 guideline-recommended follow-up test (odds ratio [OR], 1.52; 95% confidence interval [CI], 1.19 to 1.94; $P$<0.01). No statistically significant difference in receipt of ≥1 follow-up test was observed between those treated by urologists and general practitioners (OR, 1.05; 95% CI, 0.80 to 1.38; $P$=0.71). Other factors independently associated with receipt of ≥1 guideline-recommended test included age, level of comorbid illness, high-risk stone former status, medication adherence status, and type of therapy prescribed.

Figure 2 displays predicted probabilities of adherence to the different follow-up testing recommendations by specialty. In addition to the aforementioned difference in adherence to ≥1 recommendation, significant differences were observed in probability of adherence to ≥2 and all 3 recommendations (Figure 2A). Compared to urologists, general practitioners were less likely to perform a repeat 24-hour urine within 6 months; nephrologists and general practitioners were less likely to perform a subsequent 24-hour urine within 12 months; whereas nephrologists were more likely to perform drug class-specific serum testing (Figure 2B).

When increasing the time threshold for performing the repeat 24-hour urine from 6 months to 8 months, no material change in the results was observed. Specifically, relative to patients managed by a urologist, those managed by a nephrologist had higher odds of receiving ≥1 guideline-recommend follow-up test (OR, 1.50; 95% CI, 1.17 to 1.92; $P$<0.01). No significant difference between patients managed by a urologist and patients managed by a general practitioner was observed with respect to this outcome (OR, 1.05; 95% CI 0.80 to 1.38; $P$=0.71). General practitioners were still less likely than urologists to perform a repeat 24-hour urine within 8 months (14% vs. 28%, $P$<0.01), whereas no significant difference was observed between nephrologists and urologists (29% vs. 28%, $P$=0.54).

## DISCUSSION

We aimed to evaluate specialty-specific differences in adherence to follow-up testing for patients with USD prescribed PPT, including AUA guideline-recommended repeat 24-hour urine collections and drug class-specific serum tests.[3] We found that adherence to follow-up testing was low. Just over half of the cohort completed ≥1 of the guideline-recommended measures, and only 1 in 20 completed all 3. That said, there has been increasing adherence to recommended follow-up testing over time. Importantly, there are specialty-specific differences in use of on-treatment follow-up testing that may be targets for future quality improvement initiatives.

These findings build upon prior research assessing the utilization and role of metabolic testing in the diagnosis and management of USD. It has been established that rates of upfront 24-hour urine collection for patients diagnosed with USD are exceedingly low. For example, both Ganesan et al. and Hsi et al. found that few veterans with a USD diagnosis completed a 24-hour urine (15% and 8%, respectively),[11,12] whereas Milose et al. found that even fewer (7%) commercially insured adults at high risk of USD recurrence did so.[13] There also exist important differences by specialty in PPT prescription, with one recent study suggesting that veterans visiting both a urologist and nephrologist were more likely to be prescribed PPT compared to patients who visited one, the other, or neither.[14] Rates of follow-up testing among patients with known abnormalities on an initial 24-hour urine collection are also low, with 12% to 16% of such patients undergoing a repeat 24-hour urine collection within 6 months based on analyses of Litholink files.[5,6] Furthermore, several studies evaluating the impact of 24-hour urine collection following USD diagnosis on subsequent stone-related events have not detected a significant association, calling into question the role of 24-hour urine collection in tertiary prevention.[15] Based on these collective findings, we felt the need to further evaluate differences in adherence to follow-up testing by provider specialty.

To our knowledge, this is the first study to evaluate adherence to all 3 follow-up repeat 24-hour urine and serum testing recommendations in the AUA guideline.[3] The study cohort met strict criteria defining a diagnosis of USD, collection of an initial 24-hour urine, and prescription of a PPT agent. The guideline-based follow-up measures pertaining to repeat 24-hour urine collection and agent-specific serum testing were also strictly defined. Our findings have clinical practice implications. We found that even patients who undergo upfront 24-hour urine collection and are subsequently started on a PPT agent have remarkably low rates of guideline-recommended follow-up. Notwithstanding the limitations of the evidence backing the guideline statements, if guideline-based management of USD is an objective, then quality improvement is needed in this area. Specifically, urologists, nephrologists, general pracitioners, and other specialists managing USD must work together to comit to established protocols and best practices through methods such as continuing medical education, regular monitoring and feeback, and clinical decision support.[16] It should be noted, however, that adherence to ≥1 recommended follow-up measure significantly increased from 53% in 2008 to 68% in 2016, though it is unclear if this increase can be attributed to publication of the AUA guideline in 2014.[3]

The results of our study should be interpreted in the context of its limitations. The study cohort consisted of commercially insured working-age adults; consequently, the findings may not be generalizable to other populations such as uninsured or older adults. Residual confounding and omitted variable bias are possible given the observational nature of this study; however, we adjusted for numerous covariates relevant to PPT for USD including comorbidities, high-risk stone former status, medication adherence, and therapy prescribed. In spite of measures to exclude patients prescribed pharmacotherapy for other indications (i.e., hypertension and gout), it is possible some such patients were included. Furthermore, it is likely that serum testing was often performed for reasons other than kidney stone follow-up. It is also unclear to what extent providers acted on the follow-up data obtained. Associations between publication/reaffirmation of the AUA guideline and adherence to its recommendations should be examined in other cohorts. Finally, data regarding kidney stone composition and abnormal findings on 24-hour urine analyses were not analyzed because they are infrequently reported or undiscernible in the form of claims.

While one of our aims was to evaluate adherence to guideline-recommended follow-up testing for patients started on PPT in the form of 24-hour urine and serum testing—a surrogate for quality of follow-up in this population—and its relation to stone-related events, there are a number of other potential indicators of the quality of follow-up for USD tertiary prevention which were beyond the scope of this study. For example, we did not assess the frequency of follow-up testing for patients started on dietary therapy. We also did not evaluate AUA guideline-recommended follow-up pertaining to repeat stone analysis or struvite stone prevention.[3] Adherence to recommendations for repeat imaging[3] is also of interest, as one study found that fewer than half of patients in Michigan undergo follow-up imaging after ureteroscopy.[17] The extent to which follow-up evaluation and management visits correlate with claims for follow-up testing is unclear. Finally, we did not assess recurrent stone events. These are areas for future research. Regarding follow-up testing for patients started on PPT following an initial 24-hour urine collection, the optimal timing of repeat collection is unclear. Furthermore, the optimal timing of PPT agent-specific serum testing, as well as the frequency of adverse effects detected, have also not been established. Finally, the influence of adherence to recommended follow-up testing upon adherence to the therapy itself requires further evaluation.

## CONCLUSIONS

There exist significant differences between specialties in prescription of PPT and adherence to guideline-recommended follow-up testing. Adherence to such testing was low overall. Further evaluation of follow-up testing patterns for patients started on PPT is needed to better understand the impact on USD outcomes and to optimize follow-up testing protocols.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## FUNDING

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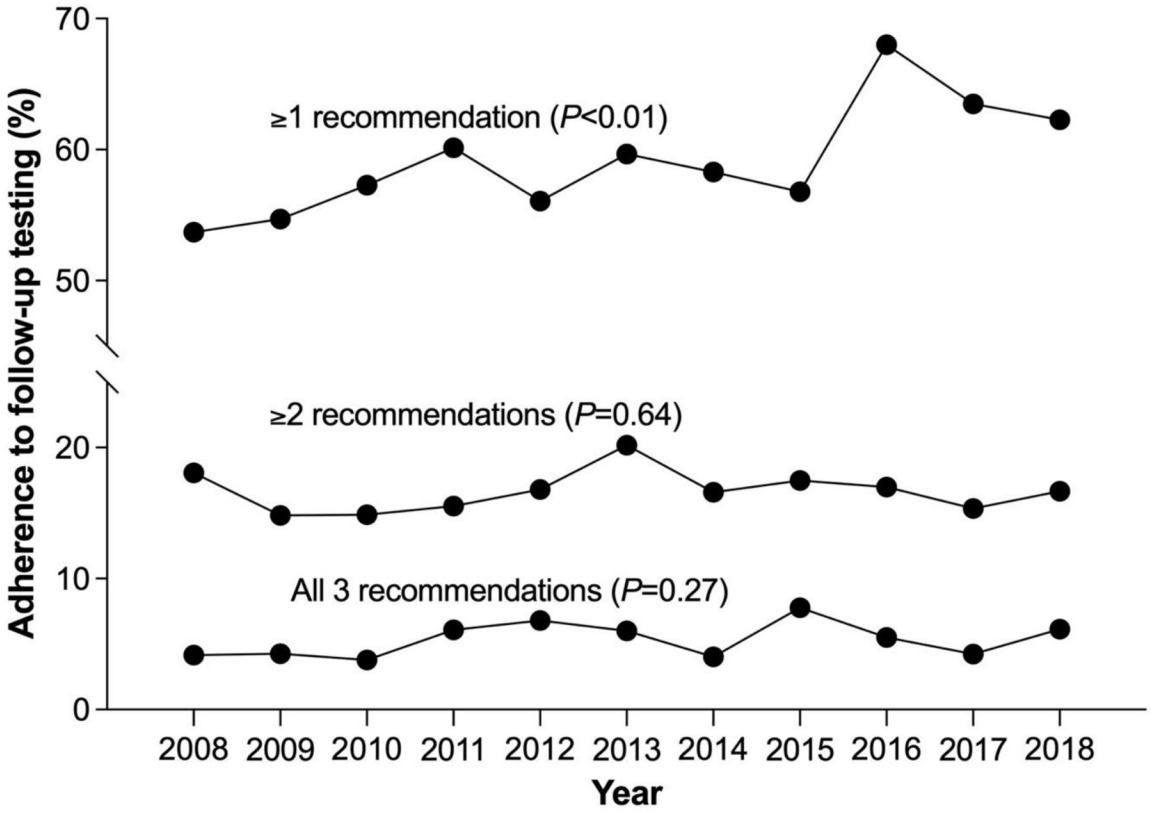


**Figure 1.**
Annual adherence to follow-up testing recommendations among 2600 patients receiving selective PPT.

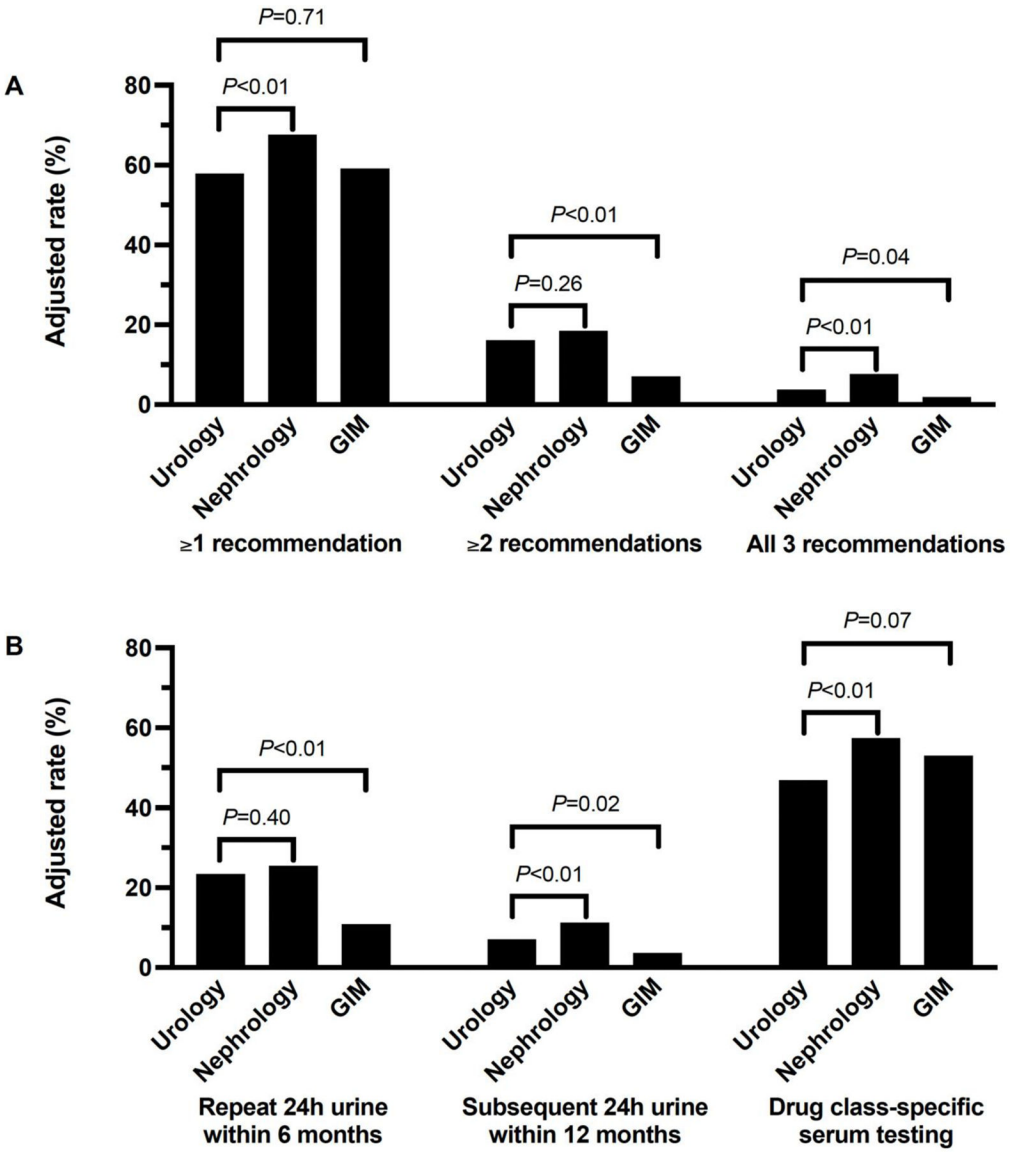


**Figure 2.**
Predicted probabilities of guideline recommendation-concordant care. GIM: general/internal medicine.

**Table 1.**

Characteristics of patients prescribed selective PPT stratified by prescribing provider specialty. IM: internal medicine.

| Characteristic | Overall (n=2600) | Prescribing provider specialty | | | |
|---|---|---|---|---|---|
| | | Urology (n=1927) | Nephrology (n=377) | General/ IM (n=296) | *P* |
| **Age in years (%)** | | | | | |
| 18–34 | 420 (16) | 312 (16) | 81 (22) | 27 (9) | <0.01 |
| 35–44 | 552 (21) | 424 (22) | 79 (21) | 49 (17) | |
| 45–54 | 839 (32) | 626 (33) | 111 (29) | 102 (35) | |
| 55–64 | 789 (30) | 565 (29) | 106 (28) | 118 (40) | |
| **Female gender (%)** | 1061 (41) | 755 (39) | 186 (49) | 120 (41) | <0.01 |
| **Race/ethnicity (%)** | | | | | |
| White | 2135 (82) | 1,591 (83) | 306 (81) | 238 (80) | 0.44 |
| Black | 159 (6) | 112 (6) | 22 (6) | 25 (8) | |
| Other | 306 (12) | 224 (12) | 49 (13) | 33 (11) | |
| **Education (%)** | | | | | |
| High school or less | 559 (22) | 433 (23) | 59 (16) | 67 (23) | 0.03 |
| Some college | 1429 (55) | 1,057 (55) | 214 (57) | 158 (53) | |
| College or more | 612 (24) | 437 (23) | 104 (28) | 71 (24) | |
| **Region of residence (%)** | | | | | |
| Midwest | 738 (28) | 530 (28) | 119 (32) | 89 (30) | <0.01 |
| Northeast | 240 (9) | 161 (8) | 46 (12) | 33 (11) | |
| South | 1190 (46) | 918 (48) | 157 (42) | 115 (40) | |
| West | 432 (17) | 318 (17) | 55 (15) | 59 (20) | |
| **Charlson Comorbidity Index, mean (SE)** | 0.32 (0.02) | 0.29 (0.02) | 0.41 (0.06) | 0.39 (0.06) | 0.02 |
| **High-risk stone former (%)** | 662 (26) | 461 (24) | 127 (34) | 74 (25) | <0.01 |
| **Medication adherence (%)** | 1175 (45) | 824 (43) | 187 (50) | 164 (55) | <0.01 |
| **Therapy prescribed (%)** | | | | | |
| Alkali citrate | 1253 (48) | 1,016 (53) | 171 (45) | 66 (22) | <0.01 |
| Uric acid reducing agent | 228 (9) | 158 (8) | 34 (9) | 36 (12) | |
| Thiazide | 738 (28) | 472 (25) | 103 (27) | 163 (55) | |
| Combination therapy | 381 (15) | 281 (15) | 69 (18) | 31 (11) | |
| **Adherence to ≥1 follow-up testing recommendation (%)** | 1523 (59) | 1,085 (56) | 256 (68) | 182 (62) | <0.01 |
| **Adherence to ≥2 follow-up testing recommendations (%)** | 429 (17) | 321 (17) | 79 (21) | 29 (10) | <0.01 |
| **Adherence to 3 follow-up testing recommendations (%)** | 137 (5) | 88 (5) | 39 (10) | 10 (3) | <0.01 |

**Table 2.**

Multivariable logistic regression model predicting odds of adherence to at least one guideline-recommended follow-up test. IM: internal medicine.

| Characteristic | Odds ratio | 95% confidence interval | *P*-value |
|---|---|---|---|
| **Age in years** | | | |
| 18–34 | Ref. | | |
| 35–44 | 1.08 | 0.83 to 1.40 | 0.58 |
| 45–54 | 1.28 | 1.00 to 1.64 | 0.05 |
| 55–64 | 1.53 | 1.18 to 1.97 | <0.01 |
| **Female gender** | 1.03 | 0.87 to 1.23 | 0.71 |
| **Race/ethnicity** | | | |
| White | Ref. | | |
| Black | 0.97 | 0.69 to 1.35 | 0.84 |
| Other | 1.22 | 0.94 to 1.58 | 0.13 |
| **Education** | | | |
| High school or less | Ref. | | |
| Some college | 0.89 | 0.72 to 1.10 | 0.30 |
| College or more | 1.03 | 0.81 to 1.32 | 0.79 |
| **Region of residence** | | | |
| Midwest | Ref. | | |
| Northeast | 1.06 | 0.77 to 1.46 | 0.71 |
| South | 1.04 | 0.85 to 1.27 | 0.69 |
| West | 1.15 | 0.89 to 1.49 | 0.27 |
| **Charlson Comorbidity Index (per 1 unit increase)** | 1.31 | 1.16 to 1.47 | <0.01 |
| **High-risk stone former** | 1.46 | 1.19 to 1.78 | <0.01 |
| **Medication adherence** | 2.06 | 1.74 to 2.44 | <0.01 |
| **Therapy prescribed** | | | |
| Uric acid reducing agent | Ref. | | |
| Thiazide | 1.72 | 1.27 to 2.35 | <0.01 |
| Alkali citrate | 1.53 | 1.14 to 2.06 | <0.01 |
| Combination therapy | 2.18 | 1.54 to 3.08 | <0.01 |
| **Provider specialty** | | | |
| Urology | Ref. | | |
| Nephrology | 1.52 | 1.19 to 1.94 | <0.01 |
| General/IM | 1.05 | 0.80 to 1.38 | 0.71 |