Published in final edited form as:

Nephrology (Carlton). 2016 October ; 21(10): 851–859. doi:10.1111/nep.12676.

Clinical Predictors of Diagnostic Testing Utility in the Initial Evaluation of Chronic Kidney Disease

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Abstract

Aim—No evidence-based approach to the evaluation of CKD has been established. We sought to identify clinical criteria to guide a rational diagnostic approach for the initial evaluation of CKD.

Methods—We conducted a retrospective cohort study of 1,487 patients presenting for initial evaluation of CKD over three years (1/2010–1/2013) to academic nephrology clinics. We utilized the electronic medical record to determine tests ordered, abnormal results, and testing that affected diagnosis and/or management. Diagnostic and management yield of testing was defined as the percentage of tests that affected diagnosis and/or management. High yield for a given test was defined as an increased likelihood of the test affecting diagnosis and/or management.

Results—We identified clinical criteria predictive of high yield for paraprotein-related testing (one of the following: history of monoclonal disease, high risk of CKD progression, hypercalcemia or hemoglobin <10.6), and clinical criteria predictive of high yield for glomerulonephritis testing (one of the following: abnormal urine sediment, 3+ or greater hematuria or proteinuria >500mg/gm). A prior history of hydronephrosis and renal artery stenosis was predictive of high yield of abnormal renal ultrasound. Higher yield of testing was associated with higher risk progression categories for ANA, SPEP, urine sediment, calcium, PTH, hemoglobin, iron, and ferritin. We estimate that initial CKD evaluation costs range from \$28 to \$109 million/year in US-Medicare expenditure.

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Author Contributions: Drs. Mendu and Waikar take responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Mendu, Robinson

Analysis and interpretation of data: Mendu, Aizer, Waikar

Drafting of the manuscript: Mendu, Waikar, Steele, Robinson, Lundquist, Leaf

Critical revision of the manuscript for important intellectual content: Mendu, Waikar

Statistical analysis: Mendu, Aizer, Waikar

Administrative, technical, or material support: Waikar

Study supervision: Waikar

Competing Interests: All authors state that they have no competing interests.

Conclusion—Numerous tests without significant clinical utility are obtained in initial CKD evaluation. Identifying criteria that can guide diagnostic testing may lead to a more informed and cost-effective approach to evaluation.

Keywords

Chronic Renal Insufficiency; Kidney Disease

Background

Chronic kidney disease (CKD) affects approximately 13% of adults in the United States (US), over 10% of the global population, and is associated with significant morbidity, mortality and healthcare costs.^{1–6} The incidence and prevalence of CKD have risen dramatically, partly due to the increasing prevalence of diabetes and hypertension.³ The differential diagnosis for CKD is broad and includes diabetes, hypertension, primary and secondary glomerulonephritis, tubulointerstitial disease, vascular disease, urological causes and unknown.² A number of laboratory and imaging tests are available to determine the etiology of CKD. Despite the pervasiveness and impact on healthcare costs, no evidence-based approach to evaluating CKD has been established.

Consensus-based recommendations exist from national and international organizations such as the Kidney Disease Improving Global Outcomes (KDIGO)^{7,8} and the Kidney Disease Outcomes Quality Initiative (KDOQI).² KDIGO recommends evaluating “the clinical context” and obtaining a urinalysis, renal ultrasound, serum and urine electrolytes in most patients.^{7,8} KDOQI recommends clinical clues to potential diagnoses to guide evaluation and recommends that all patients have a serum creatinine, urine protein, urine sediment or urine dipstick, renal ultrasound and serum electrolytes.² Reviews aimed at primary care physicians (PCPs) outline a broad list of potential diagnoses and testing, without guidance regarding when to utilize certain tests.⁹

We recently found that numerous tests are ordered in the initial evaluation of CKD despite low diagnostic yield.¹⁰ The tests with the highest yield for diagnosis and/or management were hemoglobin A1c and urine protein quantification. Tests that had low yield included renal ultrasonography, testing for paraprotein-associated kidney disease, and serologic testing for glomerular diseases. To investigate these tests further and to clarify their role in the diagnostic evaluation of CKD, we sought to identify the factors associated with a higher yield, defined as testing that affected diagnosis and/or management. We developed a framework to guide providers regarding testing decisions in the initial evaluation of CKD. Finally, we also calculated the US-Medicare reimbursement costs associated with CKD evaluation testing.

Methods

Study Design and Patient Population

We identified patients referred (primarily by primary care providers within the same hospital network) for initial evaluation of CKD between January 1, 2010– January 1, 2013 to

nephrology clinics affiliated with Brigham and Women's Hospital (BWH) and Massachusetts General Hospital (MGH) in Boston, MA. The institutional review board approved the study and waived the need for consent. Patients were excluded if evaluated for a second opinion, had another reason for referral (i.e. uncontrolled hypertension, hyperkalemia etc.), or were re-establishing care. Of 3,829 patients identified by the clinics' internal records of patient referrals, 1,487 patients were included in the final analysis.

Data Sources and Collection

The BWH/MGH Research Patient Data Registry and electronic medical record were utilized to abstract data from nephrology and primary care progress notes, laboratory and imaging results by author MM. We used methods recommended to ensure the validity and reliability of data collected, including a standardized abstraction database, precisely defined variables and criteria, and review by two authors (MM and SW) of ten initial charts to refine criteria.¹¹ Data collected included demographics, visit dates, comorbidities, initial medications, blood pressures, labs, imaging, biopsies, need for renal replacement, and medication changes. We documented whether a test was obtained by another provider, such as a PCP or urologist, prior to the nephrology visit. All nephrology progress notes were manually reviewed to ascertain whether a test was documented to affect diagnosis and/or management, the presumed etiology of CKD and specific management decisions.

Criteria for Diagnostic Testing

Abnormal findings for labs were based on the reference range established by the BWH and MGH laboratories. An abnormal finding for imaging was defined as any abnormality reported in the final report, with the exception of simple cysts and non-obstructing stones for renal ultrasound. Tests were considered to have affected diagnosis if it was specifically stated in the nephrology progress notes to contribute to, confirm, or establish the underlying etiology of CKD. Tests were considered to have affected management if it was specifically stated in the nephrology progress notes to contribute to, confirm, or establish any management decision. These definitions included negative and positive test results and all diagnoses related to CKD. A blind abstraction of 36 random patients' records (2.4% of the total number of patients) was conducted by a second reviewer (author ER). Inter-rater agreement, assessed by the prevalence-adjusted, bias-adjusted kappa statistic,^{12,13} was mean of 0.89 (standard error of 0.015) for the diagnostic test variables.

Clinical Utility

We determined the frequency and yield of CKD diagnostic testing stratified by KDIGO 2012 risk categories (defined based on estimated glomerular filtration rate (eGFR) and albuminuria).⁷ Clinical criteria for the diagnostic/management yield of tests for paraprotein-associated kidney disease glomerular diseases [serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP), serum free light chains (FLC) and serologic tests such as antinuclear antibody (ANA), complement component 3 (C3), complement component 4 (C4), double stranded DNA (DsDNA), Anti-Ro Antibody (Ro), and Anti-La Antibody (La)] were identified based on clinical features associated with multiple myeloma and immune-related kidney disease described in previous literature.¹⁴⁻¹⁶

Statistical Methods

Categorical variables were reported as percentages and compared using Fisher's exact test and the chi-square trend test as appropriate. Denominators were the number of tests obtained, and the numerators were the number of tests in which findings were abnormal or affected diagnosis and/or management. We determined clinical characteristics associated with certain tests (renal ultrasound, immunoglobulin-related testing, serologic testing) affecting diagnosis and management using Fisher's exact test. Chi-square trend tests were used to ascertain if there was an association between increasing KDIGO risk category and the frequency of testing obtained, rates of abnormal results, and diagnostic/management yield. For clinical predictors of renal ultrasound testing yield we calculated likelihood ratios and 95% confidence intervals. A two-sided $p < 0.05$ was considered statistically significant. Statistical analyses were performed using SAS version 9.3 software (SAS Institute, Cary, NC).

Cost Calculations

We calculated cost using the Centers for Medicare fee schedule for outpatient services.^{17,18} The cost per test affecting diagnosis and/or management was calculated as the total cost associated with a given test in the study divided by the number of tests that affected diagnosis and/or management. The projected annual cost for the US population was calculated as the cost per test, multiplied by the frequency of the test ordered in this study, multiplied by the estimated annual incidence of CKD in patients younger than 80; this figure was 335,961, based on Drey et al., which calculated an annual incidence rate of 1071 per million population and US census data from 2010 estimating a population of 313,696,890 younger than 80.^{19,20} We excluded patients 80 and older assuming that providers would be less likely to pursue a workup. Finally, we estimated approximately 26% of CKD patients annually would be referred to nephrology based on published referral rates;²¹ multiplying projected annual cost by 26% provided a low estimate of projected annual cost.

Results

Clinical Characteristics

Table 1 depicts characteristics of the 1,487 patients included in the study. The median age was 70 (IQR 61, 79) years and 61.4% were male. The most common comorbidities included hypertension (79.0%), diabetes (58.4%), and coronary artery disease (25.7%). The most common medications prescribed prior to the initial visit included statins (58.2%), beta-blockers (54.5%) and angiotensin-converting-enzyme inhibitors (40.9%); 13.7% were treated with nonsteroidal anti-inflammatory drugs (NSAIDs). The most frequent CKD stage was 3b (39.6%), followed by stage 3a (28.7%) and stage 4 (18.6%). Three percent of the cohort progressed to CKD stage 5 requiring renal replacement therapy during the study period.

Clinical Factors Associated with Higher Yield of Laboratory Tests

We stratified the study population based on KDIGO risk categories as shown in Figure 1. ANA, C3, C4, cryoglobulins, SPEP, UPEP, FLC, HbA1c, calcium, phosphate, PTH, 25-

vitamin D, hemoglobin, iron and ferritin were more likely to be obtained with increasing risk category. Increasing yield of testing associated with increasing risk category was found with ANA, SPEP, urine sediment, calcium, PTH, hemoglobin, iron, and ferritin. We also evaluated two sets of clinical criteria, based on published literature,^{14–16} to identify tests that had high yield for the diagnosis of paraprotein-related kidney disease and glomerulonephritis (Table 2). The tests examined were SPEP, UPEP or FLC for paraprotein-related kidney disease, and ANA, C3, C4, DsDNA, anti-Ro and anti-LA for glomerulonephritis. A high yield for paraprotein-related kidney disease was observed when any one of the following criteria were met: history of monoclonal disease, KDIGO risk stage 4 (based on eGFR and proteinuria), hypercalcemia (serum calcium >10.7) or anemia (hemoglobin < 10.6). These criteria identified 21 of 22 patients who had a positive SPEP, UPEP, or FLC that led to a diagnosis or management decision; one patient that did not meet either criteria was diagnosed with suspected IgA nephropathy based on mildly decreased IgA. Of note, we also looked at laboratory criteria alone and found that all 21 patients met the following: either eGFR < 45 ml/min/1.73 m² or > 1 gram of urine protein (on spot and/or 24 hour urine total protein or microalbumin). A high yield for glomerulonephritis testing was observed when any of the following clinical criteria were met: abnormal urine sediment (any finding other than an acellular sediment or epithelial cells), 3+ or greater hematuria or proteinuria >500mg (per gm creatinine on spot and/or per day 24 hour urine total protein or microalbumin). All 11 patients who were diagnosed with glomerulonephritis had at least one of these laboratory abnormalities. The majority of patients who underwent glomerulonephritis laboratory testing (306 of 493) had none of these laboratory abnormalities, and none led to a diagnosis or management decision. Of note, ANCA and anti-GBM were not abnormal and did not affect diagnosis and/or management in any cases.

Renal Ultrasound Testing Characteristics

Results of renal ultrasound testing are shown in Table 3. The most common abnormal findings among the 1007 patient who had renal ultrasound were increased echogenicity (10.3%), renal artery stenosis (4.3%), and cortical thinning (4.3%), and 59 led to a diagnosis (27 with hypertensive nephrosclerosis, 16 with renovascular related and 13 with hydronephrosis). Results of renal ultrasound led to a new and unsuspected diagnosis of polycystic kidney disease in one case. In 12 cases, the diagnosis of previously unsuspected obstructive uropathy was made (4 were severe, and 2 resulted in urologic intervention). The most common management decisions based on renal ultrasound were stopping or avoiding angiotensin-converting-enzyme inhibitors and angiotensin receptor blockers, blood pressure control, and urology referral/intervention. Higher yield was observed in patients with a history of hydronephrosis or renal artery stenosis (+LR 12.7, +LR 8.3, respectively, $p < .001$); 7 of 65 who had a high yield ultrasound had a history of hydronephrosis (8 out of 942 patient who did not have a high yield ultrasound had a history of hydronephrosis), and 4 of 65 patients who had a high yield ultrasound had a history of renal artery stenosis (7 out of 942 patient who did not have a high yield ultrasound had a history of renal artery stenosis).

Proposed Framework for CKD Evaluation

Table 4 illustrates common examples of diagnoses and management decisions for testing obtained in evaluating CKD. For example, patients who had a LDH or haptoglobin affect

diagnosis and/or management were diagnosed with tacrolimus related thrombotic microangiopathy and had tacrolimus discontinued. Based on the findings in this study, we have proposed a diagnostic framework for providers evaluating patients with CKD (Figure 2).

Diagnoses and Management Decisions

The most common etiologies documented as the presumed cause of CKD were hypertensive nephrosclerosis (41.2%), diabetic kidney disease (26.8%), and vascular disease (13.3%). The diagnosis was listed as unknown in 16.4% (supplementary eTable 2). A total of 70 patients underwent kidney biopsy (supplementary eTable 1). The most common biopsy findings included secondary focal segmental glomerulosclerosis (41.4%), arteriosclerosis (22.9%) and diabetic nephropathy (22.9%). The most commonly started medication were Vitamin D supplementation (8.7%), ACE-I or ARB (6.6%), and active vitamin D (6.0%) (supplementary eTable 3). Management recommendations after initial evaluation of CKD included avoidance of NSAIDs (35.4%), blood pressure control (30.7%), and low sodium diet (11.2%) (supplementary eTable 4).

Cost Implications

Supplementary eTable5 shows the cost in Medicare expenditure of testing in the initial evaluation of CKD. The cost per test that affected diagnosis and/or management ranged from \$2677 for renal ultrasound to \$30 for urine total protein to creatinine. We extrapolated our findings to the US population and found that the initial evaluation of CKD patients annually would be close to \$109 million if all patients who developed CKD were evaluated for the condition. We calculated a low estimate of annual cost of \$28.0 million, based on an estimation of CKD patients who would be referred to nephrology. Excluding the highest yield tests such as HbA1c and urine quantification studies, cost of CKD evaluation ranges from \$27 million to \$106 million; therefore, a more stringent approach to testing utilization for CKD evaluation could lead to significant cost savings.

Discussion

In this analysis of patients presenting for an initial evaluation of CKD, we have identified that certain clinical criteria—such as the presence of an abnormal urine sediment, hematuria or proteinuria for glomerulonephritis testing; the presence of monoclonal disease, KDIGO risk stage 4, hypercalcemia or anemia for paraprotein testing—were associated with higher yield for testing related to paraprotein-associated kidney disease or glomerulonephritis. For renal ultrasound, having a prior history of hydronephrosis or a prior history of renal artery stenosis increased the likelihood of the test contributing to determining the etiology of CKD. We also calculated that the annual Medicare expenditure on CKD evaluation testing is close to \$109 million if all patients who develop the condition annually are evaluated. Notably, this figure does not include the cost of additional follow-up testing and monitoring (e.g., bone marrow biopsy in patients with an abnormal SPEP, repeating the renal ultrasound in patients with hydronephrosis, etc.). Finally, we have developed a framework based on our findings to guide providers evaluating patients with CKD.

Few studies have examined testing related to CKD. A survey of 301 physicians, presented a hypothetical CKD patient, showed that 47% of nephrologists and 33% of internists could identify five of six tests indicated by KDOQI guidelines;²² 85% of physicians recommended at least 1 additional test (such as SPEP, uric acid, ANA), accounting for a 23% increase in per-patient cost. One study examined the utility of SPEP in 2544 patients being evaluated for CKD and found that 63.2% had the test obtained and no patient had the test affect diagnosis.²³ Another study evaluated the role of SPEP and UPEP in 165 males with nephrotic range proteinuria, and myeloma was diagnosed with 1.2% of patients, with a cost per case of myeloma or MGUS of \$1,192.²⁴

Our study raises a number of important issues related to diagnostic testing in CKD. First, most testing does not have high utility which can drive up healthcare costs. It may be that with the lack of an evidence-based approach to diagnostic evaluation, providers err on the side of being comprehensive when obtaining testing, but ordering tests increases physicians' time demands. Renal ultrasound was one of the most commonly ordered tests. The majority of abnormal findings were non-specific, such as increased echogenicity and cortical thinning, and most common diagnoses in patients whose ultrasounds affected diagnosis were hypertension and renovascular disease. However, there was 1 new diagnosis of polycystic kidney disease and 2 new diagnoses of severe hydronephrosis warranting urologic intervention. Though we were able to identify that a history of hydronephrosis and a history renal artery stenosis were predictors of a higher yield diagnostic renal ultrasound, further study in the form of a cost-effectiveness analysis may be warranted. We stratified the patient population based on KDIGO risk categories for CKD progression to determine if increasing risk category results in higher yield. While we found this to be the case for labs related to CKD management (hemoglobin, iron, ferritin, PTH) and certain diagnostic labs (urine sediment, SPEP, and HbA1c) increased risk category was not associated with greater yield for most tests. Even for patients in the very high risk category, reflexively ordering a large number of tests may not be the optimal approach to CKD evaluation. For glomerular diseases or paraprotein-related diseases, relevant laboratory and clinical clues greatly increased the yield of diagnostic testing. The majority of patients in this study who underwent diagnostic testing for glomerulonephritis, for example, had neither an abnormal urine sediment or significant hematuria or proteinuria.

Our results suggest that the potential price tag for CKD testing in the US annually may be approximately \$109 million (compared to the annual allocation of the National Institutes of Health funds to kidney, urologic and hematologic research of \$418 million).²⁵ CKD evaluation, like in other areas of medicine,^{26,27} may represent an opportunity for cost savings through optimizing diagnostic testing strategies.

The major limitation of this study is the subjective nature of evaluating whether a test affected diagnosis or management, based on the interpretation of nephrology progress notes. We sought to address this by undertaking an initial review of 10 charts and ensuring that there was agreement by two of the authors, both nephrologists, of testing criteria. We also ensured that another nephrologist, not involved in the study design reviewed a subset of patient records, and we found significant agreement between reviewers based on the kappa statistic. Other limitations include the potential underestimation of diagnostic yield due to

lack of documentation surrounding decision making, limited generalizability due to the inclusion of academic medical centers, and calculation of costs using Medicare charges not being reflective of the true cost of the testing to the hospital and not being generalizable to countries with low gross domestic product (GDP) compared to the United States. We provided a high and low estimate for national annual costs associated with CKD evaluation as it unclear how often patients who develop CKD undergo evaluation for the condition. Assuming all patients who develop CKD would obtain a diagnostic evaluation provides an overestimate. Assuming that only patients who are referred to nephrology will have diagnostic testing for the condition provides an underestimation of cost since tests be ordered again for monitoring, and some CKD evaluation may be done by PCPs without referral to nephrology clinics. Given the limited generalizability of our findings to countries with low GDP, we would propose additional investigations in diverse settings.

In conclusion, diagnostic testing in CKD is frequently of low-yield. We have identified clinical criteria that may guide diagnostic testing strategies, improve the yield and lower the costs of the initial evaluation of CKD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding/Support: There was no external financial support for this study.

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Low Risk				Moderate Risk				
	Obtained	Abnormal	Affects Diagnosis/ Management		Obtained	Abnormal	Affects Diagnosis/ Management	
Renal US	68.3%	8.9%	3.6%	Renal US	65.4%	18.1%	6.2%	
ANA	35.4%	41.4%	0%	ANA	22.1%	49.3%	4.2%	
C3	22.0%	16.7%	0%	C3	22.2%	5.6%	0%	
C4	22.0%	22.2%	0%	C4	22.1%	4.2%	0%	
DsDNA	12.2%	0%	0%	DsDNA	10.0%	3.1%	3.1%	
Cryo	4.9%	0%	0%	Cryo	2.5%	0%	0%	
SPEP	59.8%	2.0%	0%	SPEP	62.9%	9.4%	1.5%	
UPEP	28.1%	0%	0%	UPEP	34.9%	3.6%	0.9%	
FL	18.3%	26.7%	0%	FL	19.3%	22.6%	0.3%	
Urine Sed	70.7%	3.5%	1.7%	Urine Sed	75.4%	7.4%	3.3%	
Udip heme	65.9%	7.4%	3.7%	Udip heme	68.5%	10.5%	2.2%	
HbA1c	11.0%	11.1%	0%	HbA1c	8.7%	28.6%	14.2%	
Uric Acid	35.4%	20.7%	6.9%	Uric Acid	20.9%	28.4%	7.5%	
Calcium	95.1%	2.6%	0%	Calcium	92.8%	4.0%	1.0%	
Phosphate	76.8%	25.4%	1.6%	Phosphate	77.0%	19.0%	1.2%	
PTH	51.2%	28.6%	2.4%	PTH	63.9%	33.7%	2.4%	
25-Vit D	45.1%	54.1%	18.9%	25-Vit D	44.9%	3.9%	11.1%	
Hb	79.3%	10.8%	0%	Hb	78.2%	17.1%	2.0%	
Fe	24.4%	5.0%	0%	Fe	27.1%	4.6%	11.5%	
Ferritin	22.0%	22.2%	0%	Ferritin	26.8%	11.6%	10.5%	
High Risk				Very High Risk				
	Obtained	Abnormal	Affects Diagnosis/ Management		Obtained	Abnormal	Affects Diagnosis/ Management	p-values
Renal US	65.6%	30.1%	7.8%	Renal US	70.8%	13.0%	5.9%	0.15,<.001, 0.72
ANA	24.7%	54.2%	0.8%	ANA	34.0%	52.2%	1.0%	<.001,0.06, 0.01
C3	20.4%	8.1%	0.8%	C3	28.8%	5.8%	0.6%	0.01,0.48, 0.59
C4	20.4%	10.1%	3.0%	C4	28.6%	7.0%	0.6%	0.01,0.10, 0.88
DsDNA	6.2%	10.0%	0%	DsDNA	9.4%	8.9%	1.8%	0.56, 0.20, 0.68
Cryo	4.1%	10.0%	15.0%	Cryo	7.0%	2.4%	2.4%	0.008, 0.97, 0.81
SPEP	65.6%	7.8%	0.6%	SPEP	73.9%	8.8%	3.6%	<.001, 0.43, 0.01
UPEP	31.7%	2.0%	0.7%	UPEP	39.6%	6.8%	3.0%	0.02, 0.04, 0.08
FL	22.8%	44.1%	0.3%	FL	31.1%	54.3%	1.9%	<.001,<.001, 0.15
Urine Sed	77.8%	8.2%	0.8%	Urine Sed	72.6%	12.2%	7.1%	0.58,0.006, 0.008
Udip heme	68.1%	10.9%	2.1%	Udip heme	72.6%	22.1%	39.5%	0.09,<.001, 0.5
HbA1c	11.3%	32.7%	5.4%	HbA1c	16.1%	46.9%	25%	0.002,.007, 0.01
Uric Acid	25.5%	47.6%	8.9%	Uric Acid	28.4%	51.8%	12.9%	0.32, <.001, 0.21
Calcium	93.8%	6.4%	0.7%	Calcium	96.7%	13.8%	0.5%	0.03,<.001, 0.97
Phosphate	84.8%	13.8%	1.0%	Phosphate	87.0%	18.1%	2.3%	<.001, 0.39, 0.76
PTH	72.8%	54.0%	8.8%	PTH	84.0%	69.1%	13.3%	<.001,<.001,0.04
25-Vit D	52.9%	36.2%	10.5%	25-Vit D	63.4%	48.3%	18.2%	<.001,0.16, 0.09
Hb	82.7%	27.6%	4.8%	Hb	88.8%	43.1%	12.6%	<.001, <.001,<.001
Fe	33.1%	9.9%	9.3%	Fe	47.3%	11.0%	20.8%	<.001, 0.04, <.001
Ferritin	31.3%	10.5%	9.9%	Ferritin	46.3%	6.1%	20.2%	<.001, 0.14, <.001

Figure 1. Frequency and yield of CKD diagnostic testing stratified by KDIGO 2012 stratified by risk categories

Abbreviations: CKD, chronic kidney disease; KDIGO, Kidney Disease Improving Global Outcomes; N, Number; %, Percentage; Renal US, Renal ultrasound; ANA, antinuclear antibody; C3, complement component 3; C4, complement component 4; DsDNA, Double stranded DNA; Cryo, cryoglobulins; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis; FL, serum free light chains; Urine sed, urine sediment; Udip heme, urine dipstick for blood; HbA1c, hemoglobin A1c; PTH, parathyroid hormone; Hb, hemoglobin; Fe, iron

Bolded results indicate an association increasing risk category and frequency of testing obtained, abnormal and affecting diagnosis and/or management.

†.Low Risk (Green)- GFR > 60 ml/min/1.73 m² and proteinuria <30 mg/g, <3mg/mmol

b.Moderate Risk (Yellow)- GFR > 60 ml/min/1.73 m² and proteinuria 30 – 300mg/g, 3–30mg/mmol, GFR 45–59 ml/min/1.73 m² and proteinuria <30 mg/g, <3mg/mmol

c. High Risk (Orange) GFR 30–44 ml/min/1.73 m² and proteinuria <30 mg/g, <3mg/mmol, GFR 45–59 ml/min/1.73 m² and proteinuria 30–300mg/g, 3–30mg/mmol, GFR>60 ml/min/1.73 m² and proteinuria >300mg/g, >30mg/nmol

d.Very High Risk (Red) GFR 0–29 ml/min/1.73 m² and proteinuria <30 mg/g, <3mg/mmol, GFR 30–44 ml/min/1.73 m² and proteinuria 30–300mg/g, 3–30mg/mmol, GFR 45–59 ml/min/1.73 m² and proteinuria >300mg/g, >30mg/nmol

e. The denominator for the percentages provided is the number of patients in the risk category (low risk- denominator equals 82, moderate risk- denominator equals 321, high risk- denominator equals 486, very high risk- denominator equals 598).

f. The denominator for the percentages provided is the number of tests obtained.

g. The denominator for the percentages provided is the number of tests obtained.

Suggestions for diagnostic evaluation in patients initially presenting for CKD workup:

- Obtain urinalysis, urine sediment, spot urine protein quantification testing (urine microalbumin to creatinine ratio or urine protein to creatinine ratio) and HbA1c if history of diabetes or clinical suspicion of diabetes.
- Obtain renal ultrasound, particularly if there is any prior history of hydronephrosis or prior history of renal artery stenosis.
- Obtain paraprotein testing including SPEP, UPEP, FL if the patient meets one of the following: established monoclonal disease, KDIGO Risk stage 4,^a Hypercalcemia,^b Anemia.^c
- Obtain serologic testing including ANA, C3, C4, DsDNA, Ro, La if the patient meets one of the following: abnormal urine sediment, 3+ or greater hematuria or proteinuria. Consider testing with ANCA, Anti-GBM based on clinical context.
- Consider additional testing with HBV, HCV, Cryoglobulins based on clinical context (history of drug use, abnormal liver function, arthralgias, rash)
- Consider additional testing with haptoglobin, LDH based on clinical context (history of medications such as tacrolimus that can cause thrombotic microangiopathy)
- Consider additional testing with renal nuclear scan or abdominal CT based on clinical context (suspicion for renal artery stenosis, atrophic kidney, obstruction).

Figure 2. Proposed Framework for the Initial Diagnostic Evaluation of Chronic Kidney Disease

Abbreviations: N, Number; %, Percentage; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis; ANA, antinuclear antibody; C3, complement component 3; C4, complement component 4; HCV, hepatitis C testing; HBV, hepatitis B testing; ANCA, Anti-neutrophil cytoplasmic antibody; LDL, Low-density lipoprotein; DsDNA, Double stranded DNA; Anti-GBM, Anti-Glomerular basement membrane antibody; Abdominal CT, Abdominal computed topography; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; MRA, magnetic resonance angiogram; N/A, not applicable

a. KDIGO risk stage 4 (very high risk) GFR 0–29 ml/min/1.73 m² and proteinuria <30 mg/g, <3mg/mmol, GFR 30–44 ml/min/1.73 m² and proteinuria 30–300mg/g, 3–30mg/mmol, GFR 45–59 ml/min/1.73 m² and proteinuria >300mg/g, >30mg/nmol

b. Hypercalcemia- defined as a serum calcium greater than 10.7

c. Anemia-defined as a hemoglobin less than 10.6

Table 1

Patient demographics and clinical characteristics

Patient Characteristics	N (%)
Male	914 (61.4)
Age, median (IQR)	70 (61,79)
Married or with Partner	845 (56.8)
English speaking	1402 (94.3)
Race	
White	1084 (72.9)
African American	189 (12.7)
Hispanic	149 (10.0)
Comorbidities	
Hypertension	1175 (79.0)
Diabetes	868 (58.4)
Coronary artery disease	382 (25.7)
History of malignancy	359 (24.1)
Gout	207 (13.9)
Anemia	182 (12.2)
Obesity	164 (11.0)
Congestive heart failure	142 (9.6)
Benign prostatic hypertrophy	139 (9.4)
Kidney stones	130 (8.7)
Connective tissue disease	60 (3.4)
Nephrectomy	44 (3.0)
Monoclonal disease	41 (2.8)
Lupus	18 (1.2)
History of hydronephrosis	18 (1.2)
History of renal artery stenosis	13 (0.9)
CKD Stage[†]	
CKD Stage 1–2	183 (12.3)
CKD Stage 3a	427 (28.7)
CKD Stage 3b	589 (39.6)
CKD Stage 4	276 (18.6)
CKD Stage 5	12 (0.8)
Medications prior to initial visit	
Statins	865 (58.2)
Beta-blockers	810 (54.5)
Angiotensin-converting-enzyme inhibitors	608 (40.9)
Calcium channel blockers	531 (35.7)

Patient Characteristics	N (%)
Proton pump inhibitors	426 (28.7)
Thiazides	378 (25.4)
Loop diuretics	307 (20.7)
Angiotensin receptor blockers	306 (20.6)
Vitamin D supplementation	245 (16.5)
Nonsteroidal anti-inflammatory drugs	203 (13.7)
Allopurinol	147 (9.9)
Required renal replacement therapy during study period	
Dialysis	40 (2.7)
Transplant	4 (0.3)

Values represent N (%) unless otherwise stated.

Abbreviations: CKD, Chronic Kidney Disease

[†]Based on most recent estimated glomerular filtration (eGFR) rate prior to study enrollment period

CKD stage 1–2 eGFR >60 ml/min per 1.73m², stage 3a eGFR 45–59 ml/min per 1.73m², stage 3b eGFR 30–44 ml/min per 1.73m², stage 4 eGFR 15–29 ml/min per 1.73m², stage 5 GFR <15 ml/min per 1.73 m²

Table 2

Clinical criteria associated with higher yield of diagnostic testing

<u>N=1035 (obtained SPEP, UPEP or FLC)</u>	<u>Meets criteria of one of the following: Established Monoclonal Disease, KDIGO Risk stage 4, [†] Hypercalcemia, [‡] Anemia [§]</u>	<u>Does Not Meet Criteria N= 513</u>	<u>P-value</u>
SPEP or UPEP or FL affects diagnosis or management	21 (4.0%)	1 (0.2%)	0.004
SPEP or UPEP or FL does not affect diagnosis or management	501 (96.0%)	512 (99.8%)	
<u>N=493 (obtained ANA, C3, C4, DsDNA, Ro, La)</u>	<u>Meets criteria of abnormal urine sediment, [¶] 3+ or greater hematuria or proteinuria >500mg/gm N=187</u>	<u>Does Not Meet Criteria N= 306</u>	<u>P-value</u>
ANA/C3/C4/DsDNA/Ro/La affects diagnosis or management	11 (5.9%)	0 (0%)	<0.001
ANA/C3/C4/DsDNA/Ro/La does not affect diagnosis or management	176 (94.1%)	306 (100%)	

Abbreviations: SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis; FL, serum free light chains; ANA, antinuclear antibody; C3, complement component 3; C4, complement component 4; DsDNA, Double stranded DNA; Ro, Anti-Ro Antibody; La, Anti-La Antibody

[†]. KDIGO risk stage 4 (very high risk) GFR 0–29 ml/min/1.73 m² and proteinuria <30 mg/g, <3mg/mmol, GFR 30–44 ml/min/1.73 m² and proteinuria 30–300mg/g, 3–30mg/mmol, GFR 45–59 ml/min/1.73 m² and proteinuria >300mg/g, >30mg/nmol

[‡]. Hypercalcemia- defined as a serum calcium greater than 10.7

[§]. Anemia-defined as a hemoglobin less than 10.6

[¶]. Any finding other than an acellular sediment or epithelial cells

Table 3

Renal Ultrasound Characteristics

Renal Ultrasound Characteristics	N	%
Obtained	1007	67.7%
Ordered by Nephrology	711/1007	70.6%
Abnormal Findings[†]	270/1007	26.8%
Increased Echogenicity	104/1007	10.3%
Stenosis	43/1007	4.3%
Cortical Thinning	43/ 1007	4.3%
Atrophy	27/1007	2.7%
Hydronephrosis	19/1007	1.89%
Evidence of Lithium disease	2/1007	0.2%
Affected Diagnosis	59/1007	5.9%
Hypertension-related diagnosis	27/1007	
Renovascular-related diagnosis	16/1007	
Hydronephrosis/Obstruction	13/1007	
Atrophic/asymmetric/single kidney	6/1007	
Renal artery stenosis	4/1007	
Lithium use	3/1007	
Polycystic kidney disease	1/1007	
Affected Management	33/1007	3.3%
Stop/Avoid ACE-I or ARB	11/33	
Blood pressure control	9/33	
Urology referral/intervention	5/33	
Kidney Size		
Right Kidney	Median 10.3 cm (9.4, 11.2) Mean 9.7cm	
Left Kidney	Median 10.4 cm (9.3, 11.3) Mean 9.6cm	
Predictors of Renal Ultrasound Affecting Diagnosis and/or Management		
Prior history of Hydronephrosis	⁺ LR=12.7 (4.8, 33.9) ; ⁻ LR=0.9 (0.8, 1.0)	
Prior history of Renal Artery Stenosis	⁺ LR=8.3 (2.5, 27.6) ; ⁻ LR=1.0 (0.9, 1.0)	

Abbreviations: N, Number; %, Percentage; ACE-I, angiotensin converting enzyme-inhibitor; ARB, angiotensin receptor blocker;

⁺LR, positive likelihood ratio, ⁻LR, negative likelihood ratio, and 95% confidence interval presented

[†]. An abnormal finding for imaging was defined as any abnormality reported in the final report, with the exception of simple cysts and non-obstructing stones

Table 4

Examples of diagnoses and management decisions for testing obtained in evaluating CKD

Test Obtained	Diagnoses [†]	Management Decisions [‡]
Tests primarily ordered for diagnosis		
Urine sediment	Acute interstitial nephritis due to proton pump inhibitor (based on white blood cells)	Discontinuation of proton pump inhibitor
Urine dipstick for protein	Likely diabetic nephropathy	Quantification of urine protein, started ACE-I
Urine dipstick for blood	Lupus nephritis	Started on MMF and prednisone
SPEP	Likely myeloma involving kidney	Referred to oncology for bone marrow biopsy
Renal ultrasound	<i>See supplementary eTable 2</i>	<i>See supplementary eTable 2</i>
Urine microalbumin to creatinine	Diabetic nephropathy	Started ACE-I, counseled diabetic control
Urine total protein/creatinine	Diabetic nephropathy versus secondary FSGS due to obesity	Started ACE-I, counseled regarding weight loss
UPEP	Light chain deposition disease	Referred to oncology, started on chemotherapy
ANA	Lupus nephritis	Started on MMF and prednisone
Uric Acid	Hyperuricemia contributing	Started on allopurinol
Serum free light chains	Light chain deposition disease	Referred to oncology, started on chemotherapy
C3	Lupus nephritis	Started on MMF and prednisone
C4	Lupus nephritis	Started on MMF and prednisone
HBV	Hepatitis B unlikely contributing given absence of proteinuria and low levels of hepatitis B	None
HCV	Possible hepatitis C related MPGN	Referral to hepatology for anti-viral treatment of hepatitis C
ANCA	N/A	N/A
Hemoglobin A1c	Uncontrolled diabetic nephropathy	Counseled diabetic control, dietary modification
Rheumatoid factor	Possible hepatitis C related MPGN	Referral to hepatology for anti-viral treatment of hepatitis C
DsDNA	Lupus nephritis	Started on MMF and prednisone
Anti-Ro	Lupus nephritis	Started on MMF and prednisone
Anti-La	Lupus nephritis	Started on MMF and prednisone
Cryoglobulins	Possible hepatitis C related cryoglobulinemia	Started on anti-viral treatment for HCV
Ultrasound guided renal biopsy	<i>See Table 3</i>	ACE-I treatment
Anti-GBM	N/A	N/A
Abdominal CT	Obstruction related	Urology referral for intervention
Creatine Kinase	Possible rhabdomyolysis from statin	Stopped statin
Renal nuclear scan	Renal artery stenosis	Avoid ACE-I or ARB
LDH	Tacrolimus related TMA	Stopped tacrolimus
Haptoglobin	Tacrolimus related TMA	Stopped tacrolimus
Anti-phospholipid Antibody	FSGS related to anti-phospholipid antibody	Continued warfarin indefinitely
HIV	N/A	N/A
Abdominal MRI	N/A	N/A
Abdominal MRA	N/A	N/A

Test Obtained	Diagnoses [†]	Management Decisions [‡]
Tests primarily ordered for management		
Calcium	Possible hypercalcemia contributing	Held calcium supplementation
Hemoglobin	N/A	Started iron and/or ESA
Phosphate	Tenofovir related (resulted in stopping tenofovir)	Started phosphate binder
Parathyroid hormone	N/A	Started calcitriol
25-Vitamin D	N/A	Started ergocalciferol or cholecalciferol
Iron	N/A	Started oral iron
LDL	N/A	Started statin

Abbreviations: N, Number; %, Percentage; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis; ANA, antinuclear antibody; C3, complement component 3; C4, complement component 4; HCV, hepatitis C testing; HBV, hepatitis B testing; ANCA, Anti-neutrophil cytoplasmic antibody; LDL, Low-density lipoprotein; DsDNA, Double stranded DNA; Anti-GBM, Anti-Glomerular basement membrane antibody; Abdominal CT, Abdominal computed topography; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; MRA, magnetic resonance angiogram; ACE-I, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; MMF, mycophenolate mofetil; FSGS, Focal segmental glomerulosclerosis; MPGN, membranoproliferative glomerulonephritis; TMA, thrombotic microangiopathy; ESA, erythropoiesis stimulating agent

[†]. Diagnoses represent most common diagnoses provided for a specific test that affected diagnosis; “Affected diagnosis” was defined as any test result that were noted in the nephrology progress notes to have contributed to, confirmed or established any diagnosis

[‡]. Management decisions represent most common management decisions provided for a specific test that affected management; “Affected management” was defined as any test result that were noted in the nephrology progress notes to have contributed to any management decision