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ORIGINAL ARTICLE

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Significance of the pee-value: relevance of 24-hour urine studies for patients with myeloma

Kelsey H. Natsuhara[a], Chiung-Yu Huang[b], Jennifer Knoche[a], Shagun Arora[a], Alfred Chung[a], Thomas Martin[a], Jeffrey Wolf[a], Sandy W. Wong[a], Nina Shah[a] and Rahul Banerjee[c,d]

[a]Division of Hematology & Oncology, Department of Medicine, University of California San Francisco, San Francisco, CA, USA; [b]Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA, USA; [c]Division of Medical Oncology, Department of Medicine, University of Washington, Seattle, WA, USA; [d]Clinical Research Division, Fred Hutchinson Cancer Center, Seattle, WA, USA

ABSTRACT

International Myeloma Working Group (IMWG) response criteria require refrigerated 24-hour urine specimens for most patients. However, given that serum free light chain testing has been shown to outperform 24-hour urine immunofixation as a prognostic marker, the importance of maintaining urine testing options or requirements within each level of IMWG response criteria has not been investigated. We analyzed responses to induction therapy for all transplant-eligible patients with multiple myeloma at our institution over a 3-year period using traditional versus 'urine-free' IMWG response criteria (where references to urine were removed from the descriptions for every depth of response). Of 281 evaluable patients, responses changed for only 4% of patients (95% confidence interval 2–7%) using urine-free criteria. Our results call into question the continued requirement for 24-hour urine measurements as part of IMWG response assessments for all patients. Research into the prognostic performance of urine-free IMWG criteria is ongoing.

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Introduction

Response assessments for multiple myeloma (MM) are determined using updated 2016 guidelines from the International Myeloma Working Group (IMWG), which include the use of several serum and urinary biomarkers as well as measurable residual disease assessments from bone marrow aspirates [1]. While studies of novel disease monitoring technologies from the bone marrow and blood have expanded rapidly in recent years [2–5], research into urine testing and myeloma response assessments has been largely stagnant. Twenty four-hour urine assessments are cumbersome to collect for patients; this is particularly true for women patients, patients with co-morbidities or frailty, and patients without access to a dedicated refrigerator. Although 24-hour urine testing remains essential for patients with monoclonal gammopathies of renal significance such as AL amyloidosis [6,7], its importance to other patients with MM is unclear.

Previous studies have demonstrated the limited importance of negative 24-hour urine immunofixations – currently a requirement for establishing complete responses (CR) by IMWG criteria. For example, a secondary analysis of the large IFM2009 trial by Dejoie et al. found that serum free light chain (SFLC) testing provided more discriminatory power than urine assessments with regard to progression-free survival (PFS) [8]. In another subgroup analysis of patients with MM undergoing autologous stem cell transplantation (ASCT) as part of a large clinical trial, Lahuerta et al. found no difference in outcomes between patients who achieved a CR and those who achieved an 'uncertain' CR (i.e. patients who otherwise met criteria for CR, but were missing urine immunofixation studies) [9].

While these studies provide valuable insight into the limited utility of 24-hour urine testing in determining CR assessments, neither study evaluated the global impact of removing 24-hour urine assessments from all levels of IMWG response criteria. If simplified response criteria were shown to maintain the prognostic integrity of response depth and were widely adopted, this would be a clinically meaningful change for patients across the spectrum of MM. This is

CONTACT Kelsey H. Natsuhara kelsey.natsuhara@ucsf.edu 505 Parnassus Avenue, San Francisco, CA, 94143, USA
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particularly true for patients being evaluated for ASCT and for patients enrolled on clinical trials, where IMWG response criteria are generally followed more strictly. Given that patients with positive 24-hour urine testing generally have abnormal SFLC testing as well [8], we began by analyzing the specific contribution of urine testing toward determining response depth. We hypothesized that 'urine-free' IMWG criteria – namely, the systematic removal of urine testing as an option or requirement to achieve any given depth of response – would yield discordant responses in less than 10% of patients, a proportion we determined *a priori* to be clinically irrelevant given the burden imposed by 24-hour urine testing.

Materials and methods

Patient population

We reviewed the charts of all patients with newly diagnosed MM who underwent first ASCT at our academic institution between 2016 and 2019. We excluded the following populations: (1) patients with concurrent amyloid light-chain (AL) amyloidosis, given that urine protein assessments remain a critical tool for evaluation of renal responses; (2) patients with oligosecretory or non-secretory disease per IMWG criteria, given that urine testing would not be useful in response assessments regardless; and (3) patients with progressive disease (PD) during induction, given the challenges of accurately calculating response assessments in this setting. Both patients with measurable serum monoclonal (M)-proteins (≥1 g/dL) and light-chain-only (LC-only) disease were included in this study. We evaluated both serum and urine biomarkers at two time points: (1) at diagnosis, i.e. prior to treatment initiation; and (2) at follow-up, i.e. the final set of biomarkers before ASCT.

We included all patients with sufficient diagnostic and follow-up serum and urine data to calculate an IMWG response to induction therapy. We defined evaluable serum studies as documentation of either complete SFLC studies or a measurable serum M-protein by serum protein electrophoresis (SPEP) with an identifiable paraprotein by serum immunofixation (SIFE) at both time points. Evaluable urine studies were similarly based upon 24-hour urine protein electrophoresis (UPEP) and 24-hour urine immunofixation (UIFE) results. For patients who did not have complete documentation of diagnostic or follow-up 24-hour urine studies, we set the following three rules in order to include as many patients in our analysis as possible. Firstly, for patients with a positive 24-hour UPEP but missing concurrent UIFE at any timepoint, we extrapolated a positive UIFE. Secondly, for patients with a documented negative UIFE at diagnosis, a negative UIFE at follow-up was extrapolated if urine studies were not repeated and there was no evidence of PD. Thirdly, at the follow-up timepoint only, for patients with a missing 24-hour UPEP but a negative 24-hour or spot UIFE, we extrapolated a negative 24-hour UPEP. However, patients with only a negative spot UPEP at follow-up (and no spot UIFE or 24-hour urine testing) were excluded, given the increased sensitivity of UIFE compared to UPEP.

Patient data and analysis

For patients with evaluable diagnostic and follow-up urine data, we assessed responses using both traditional IMWG criteria and 'urine-free' IMWG criteria as shown in Table 1. In brief, we defined 'urine-free' IMWG criteria as the systematic removal of urine testing results as an option or requirement to achieve any given response depth including CR, very good partial response (VGPR), partial response (PR), minimal response (MR), stable disease (SD), or PD. Given that urine testing results have no impact on the distinction between CR and stringent CR, we did not calculate rates of the latter. We determined the frequency with which the assigned IMWG response category changed with the exclusion of urine data (urine-free IMWG criteria), which we deemed the 'reclassification rate.' We then categorized the directionality of response change between traditional IMWG and urine-free criteria.

Baseline characteristics were reported using descriptive statistics such as proportions, medians, and quartiles. Kruskal-Wallis rank sum tests were used to compare continuous variables, while Fisher's exact tests were used to compare categorical variables. Reclassification rates between traditional and urine-free IMWG criteria – in all patients, patients with measurable serum M-proteins, and patients with LC-only disease – were reported along with a 95% confidence interval (CI) based on the binomial distribution. In all cases, we determined *a priori* that a reclassification rate of less than 10% would be considered clinically insignificant. All analyses were performed using R version 4.1.3 (Vienna, Austria) using a two-sided *p*-value of 0.05 as a cutoff for statistical significance. Our retrospective study was approved by the University of California San Francisco Institutional Review Board.

Table 1. Traditional IMWG vs Urine-Free Criteria.

	Traditional IMWG Criteria	Urine-Free IMWG Criteria
CR	Negative serum and urine IFE <5% BMPC Disappearance of plasmacytomas LC-only: Normal serum FLC ratio	Negative serum ~~*and urine*~~ IFE <5% BMPC Disappearance of plasmacytomas LC-only: Normal serum FLC ratio
VGPR	M-protein detectable only by serum/urine IFE, not SPEP or UPEP ≥90% reduction in serum M-protein, plus urine M-protein <100 mg/24h LC-only: ≥90% reduction in difference between serum FLC	M-protein detectable only by serum~~*/urine*~~ IFE, not SPEP or ~~*UPEP*~~ ≥90% reduction in serum M-protein, ~~*plus urine M-protein < 100mg/24h*~~ LC-only: ≥90% reduction in difference between serum FLC
PR	50–89% reduction in serum M-protein, plus ≥90% reduction in urine M-protein or urine M-protein ≤200 mg/24h LC-only: 50–89% reduction in difference between serum FLC Oligosecretory: ≥50% reduction in BMPC burden and plasmacytoma size	50–89% reduction in serum M-protein, ~~*plus ≥90% reduction in urine M-protein or urine M-protein ≤ 200 mg/24h*~~ LC-only: 50–89% reduction in difference between serum FLC Oligosecretory: ≥50% reduction in BMPC and plasmacytoma size
MR	25–49% reduction in serum M-protein, and 50–89% reduction in urine M-protein ≥50% reduction in plasmacytoma size	25–49% reduction in serum M-protein, ~~and 50-89% reduction in urine M-protein~~ ≥50% reduction in plasmacytoma size

Comparison of representative traditional IMWG criteria and urine-free IMWG criteria. Traditional IMWG criteria are derived from IMWG guidelines [1], while urine-free IMWG criteria remove the option or requirement for urine testing at every level of response. For simplicity, stable disease and progressive disease are not shown.
BMPC: bone marrow plasma cell; CR: Complete Response; FLC: free light chains; IFE: immunofixation; IMWG: International Myeloma Working Group; LC-only: light chain only disease; M-protein: monoclonal protein; mg/24h: milligrams per 24 h; MR: Minimal Response; PR: Partial Response; SPEP: serum protein electrophoresis; UPEP: urine protein electrophoresis; VGPR: Very Good Partial Response.

Results

Between 2016 and 2019, 406 patients with MM underwent first ASCT at our institution (Figure 1). Fifty-nine patients were excluded due to PD during induction or oligosecretory/non-secretory disease. Of the remaining 347 patients who were evaluated for urine data, 66 patients (19%) were excluded due to missing data precluding response assessments by traditional IMWG criteria. Thus, the final sample size of our cohort was 281 patients, of whom 82 patients (29%) had complete urine data at diagnosis and follow-up. The remaining 199 patients (71%) had incomplete urine data at either diagnosis or follow-up but were still evaluable for IMWG responses using the previously defined rules. Compared to patients with sufficient data to determine any type of response ($n = 281$), the 66 excluded patients were more likely to have LC-only disease, were more likely to have been transplanted before 2018, and were more likely to have LC normalization at pre-ASCT follow-up (Table 2).

We compared patients' response classification using traditional versus urine-free IMWG criteria. Of 281 patients evaluable for responses by both traditional and urine-free IMWG criteria, 11 patients were reclassified using urine-free criteria (Figure 2A). This corresponded to a reclassification rate of 4%, with a 95% CI of 2–7%, which fell below our pre-specified 10% cutoff for clinical insignificance. Among patients with LC-only disease ($n = 63$), 9 patients were reclassified using urine-free criteria versus traditional IMWG criteria (14%, 95% CI 7–25%; Figure 2B). Conversely, among patients with a measurable serum M-protein ($n = 218$), 2 patients were reclassified using urine-free criteria versus traditional IMWG criteria (1%, 95% CI 0–3%; Figure 2C).

Next, we characterized the directionality of response changes using traditional IMWG versus urine-free criteria. Of the 11 discordant responses, 7 were superior and 4 were inferior with urine-free criteria. The distribution of responses between traditional IMWG versus urine-free criteria are shown in Supplemental Table 1. Table 3 details the rationale behind each of the 11 patients whose responses were reclassified using urine-free criteria. For example, there were 5 patients who achieved a VGPR by traditional IMWG criteria because of a positive UIFE despite having achieved all other CR criteria (i.e. negative SIFE and <5% bone marrow plasma cells); these patients were reclassified as CR using urine-free criteria. Conversely, there were 3 patients with LC-only disease who achieved CR by traditional IMWG criteria given UIFE normalization despite retaining an abnormal SFLC ratio. With urine-free criteria, these patients were reclassified as VGPR.

Discussion

In our retrospective study of over 200 patients with MM, only 4% of responses to induction therapy (95% CI 2–7% using the binomial distribution) were

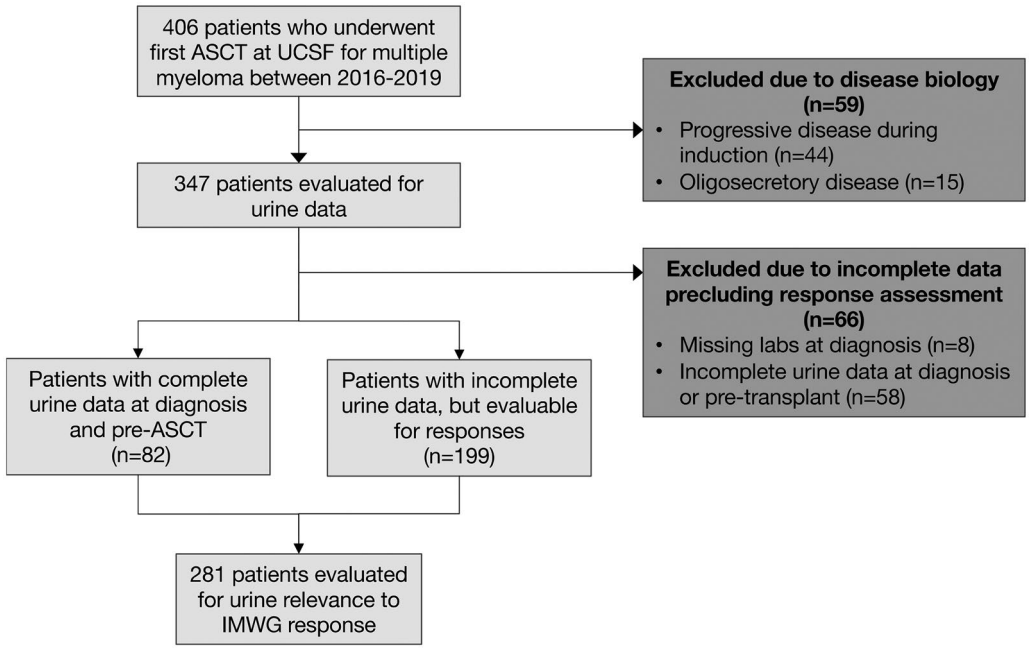

Figure 1. CONSORT Diagram. ASCT: autologous stem cell transplant; IMWG: International Myeloma Working Group.

Table 2. Baseline characteristics of patients.

Demographics	Evaluable patients ($n = 281$) median (IQR), n (%)	Non-evaluable patients ($n = 66$) median (IQR), n (%)	p value[a]
Median age at ASCT	62 (56–67)	60 (52–64)	0.01
Sex			
Female	113 (40%)	29 (44%)	0.58
Male	168 (60%)	37 (56%)	
Year of ASCT			
2016	65 (23%)	25 (38%)	
2017	55 (20%)	22 (33%)	<0.001
2018	73 (26%)	10 (15%)	
2019	88 (31%)	9 (14%)	
Years between diagnosis and ASCT	0.7 (0.6–1.0)	0.8 (0.6–1.0)	0.07
ISS stage[b]			
Stage I	75 (33%)	14 (32%)	0.13
Stage II	91 (40%)	12 (27%)	
Stage III	61 (27%)	18 (41%)	
Paraprotein nature			
Measurable M-protein	218 (78%)	23 (35%)	<0.001
LC-only	63 (22%)	43 (65%)	
FLC ratio at diagnosis[c]			
Abnormal	251 (94%)	48 (91%)	0.38
Normal	17 (6%)	5 (9%)	
FLC ratio at follow-up[c]			
Abnormal	121 (44%)	47 (80%)	<0.001
Normal	153 (56%)	12 (20%)	
UIFE at diagnosis[§]			
Positive	194 (69%)	45 (68%)	0.08
Negative	16 (6%)	0 (0%)	
Missing	71 (25%)	21 (32%)	
UIFE at follow-up[d]			
Positive	57 (20%)	21 (32%)	<0.001
Negative	219 (78%)	29 (44%)	
Missing	5 (2%)	16 (24%)	

Evaluable versus non-evaluable refers to whether sufficient data were present to calculate both traditional and urine-free IMWG responses. ASCT: autologous stem cell transplantation; FLC: free light chain; IQR: interquartile range; ISS: international staging system; LC: light chain; M-protein: monoclonal protein; UIFE: urine immunofixation electrophoresis; UPEP: urine protein electrophoresis.

[a]*p*-values are based on Kruskal-Wallis rank sum tests for continuous variables and Fisher's exact tests for categorical variables.

[b]76 patients were excluded from this analysis due to missing albumin and/or B2-microglobulin, precluding ISS reporting (54 evaluable, 22 non-evaluable).

[c]26 patients (13 evaluable, 13 non-evaluable) were missing FLC data at diagnosis. 14 patients (7 evaluable, 7 non-evaluable) were missing FLC data at follow-up.

[d]UIFE values were inferred if missing, as described in the methods. If diagnostic or pre-ASCT UPEP was positive, positive UIFE at diagnosis or pre-ASCT, respectively was assumed. If diagnostic UIFE was negative, pre-ASCT UIFE was assumed negative if not repeated.

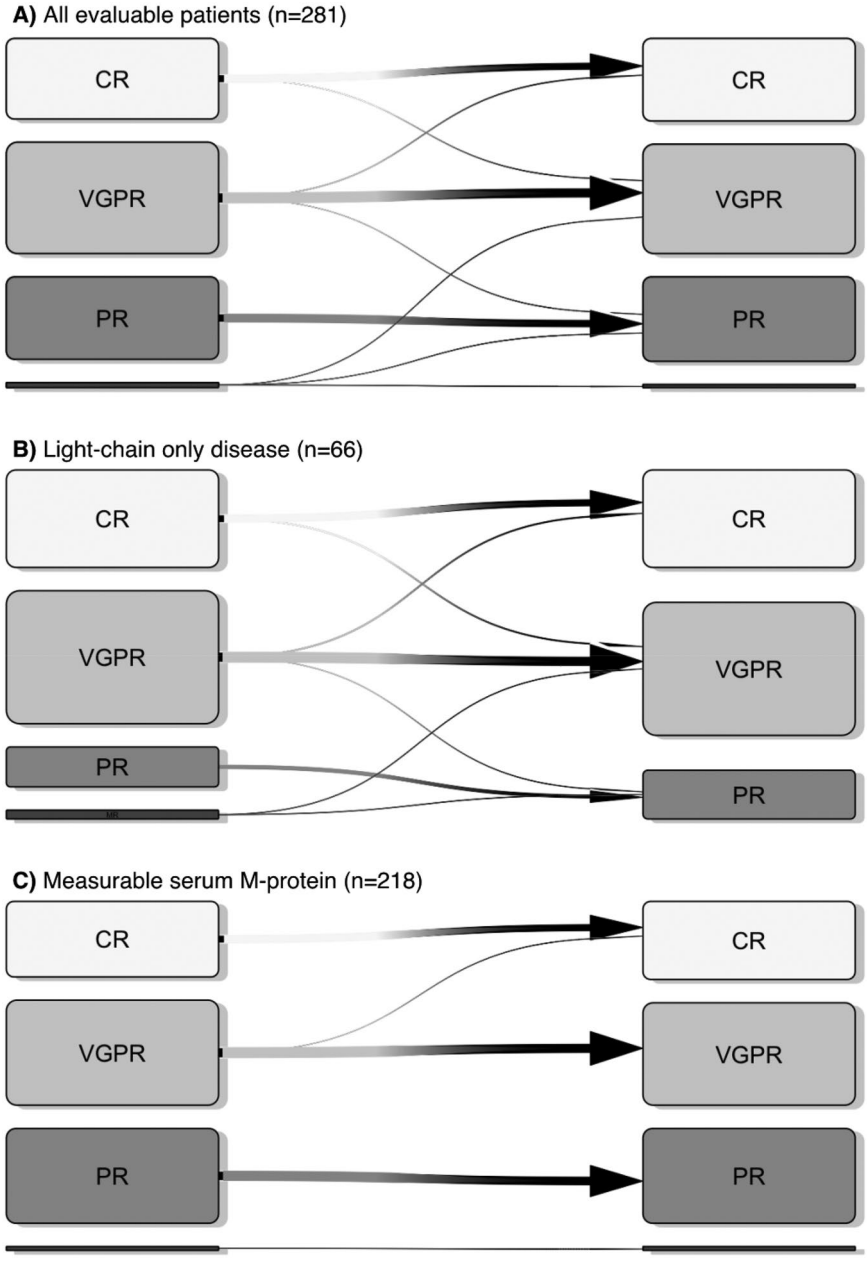

Figure 2. Response Reclassification using Traditional IMWG vs "Urine Free" Criteria. Transition plots depicting the change in response classification between traditional IMWG criteria (left panel) vs urine-free criteria (right panel). The thickness of each line represents the transition from one response category to another. CR: complete response; VGPR: very good partial response; PR: partial response; MR: minimal response (bottom row). (A) Among all evaluable patients, 11 patients were reclassified using traditional vs urine-free criteria (4% reclassification rate, 95% CI 2–7%). (B) Among patients with light-chain only disease, 9 patients were reclassified (14% reclassification rate, 95% CI 7–25%). (C) Among patients with measurable serum M-protein, 2 were reclassified (1% reclassification rate, 95% CI 0–3%).

reclassified using urine-free criteria as opposed to traditional IMWG criteria. In contrast to our expectation, omitting urine testing from IMWG response criteria did not uniformly shift responses in a more positive direction toward deeper responses. Given our hypothesis that a reclassification rate below 10% would be clinically insignificant in light of the burden of 24-hour urine testing, our results call into question the practice of requiring these assessments as part of response criteria for all patients with MM. Indeed, urine-free criteria may not only simplify response assessments but may also better reflect underlying tumor biology in the discordant cases we identified. For example, patients with LC-only MM and persistently abnormal SFLC ratios may be better classified as VGPR with urine-free criteria than as CR (if their urine testing normalized) in the current paradigm.

Table 3. Response reclassifications using traditional IMWG versus urine-free criteria.

ID	Serum M-protein	Urine M-protein	Serum free light chains	Traditional response	Urine-Free response
325	Never measurable	Measurable at Dx, then cleared	Decreased ≥90% from Dx, but remained abnormal	CR	VGPR
390	Never measurable	Measurable at Dx, then cleared	Decreased ≥90% from Dx, but remained abnormal	CR	VGPR
430	Never measurable	Measurable at Dx, then cleared	Decreased ≥90% from Dx, but remained abnormal	CR	VGPR
219	Never measurable	Measurable at Dx, but never cleared	Abnormal at diagnosis, then normalized	VGPR	CR
306	Never measurable	Measurable at Dx, but never cleared	Abnormal at diagnosis, then normalized	VGPR	CR
418	Never measurable	Measurable at Dx, but never cleared	Abnormal at diagnosis, then normalized	VGPR	CR
204	Measurable at Dx, then normalized	Measurable at Dx, but UIFE never normalized	Abnormal at diagnosis, then normalized	VGPR	CR
207	Measurable at Dx, then normalized	Measurable at Dx, but UIFE never normalized	Abnormal at diagnosis, then normalized	VGPR	CR
082	Never measurable	Measurable at Dx, but never cleared	Abnormal at diagnosis, then decreased 50–89%	VGPR	PR
217	Never measurable	Decreased 50–89% but >200mg/24h	Decreased ≥90% from Dx but remained abnormal	MR	VGPR
091	Never measurable	Decreased 50–89% but >200mg/24h	Abnormal at diagnosis, then decreased 50–89%	MR	PR

CR: complete response; Dx: diagnosis; hrs: hours; IFE: immunofixation; IMWG: International Myeloma Working Group; LC: light chain; M-protein: monoclonal protein; mg/24h: milligrams per 24 h; MM: multiple myeloma; MR: minimal response; PR: partial response; UIFE: urine immunofixation; VGPR: very good partial response.

The rationale for retaining 24-hour urine testing as part of IMWG response assessments is based on the concern that absolute measurements of free light chains in the urine and serum do not correlate sufficiently and may provide different information to guide clinical practice [10,11]. However, there is a growing body of literature that SFLC may be a more sensitive marker of disease relapse than urine studies [12,13]. While urine testing can admittedly provide insights into underlying renal pathology from glomerular or tubular dysfunction, there are multiple disadvantages to its use [7]. For example, in patients with low baseline SFLC production, urinary accumulation of light chains can make these measurements unreliable, despite a good response to therapy [14]. More importantly, 24-hour urine samples are challenging even for healthy patients to obtain in the ambulatory setting [14–16]. For patients with MM, comorbidities such as urinary incontinence or treatment-related neuropathy can complicate the process of urinating into a jug with every void over a 24-hour period. Importantly, 24-hour urine samples are anatomically more difficult to collect for women than men. Furthermore, from the standpoint of healthcare equity, the need for 24 hours' worth of access to a private refrigerator may be difficult for patients with limited means to take time off from work or to work from home.

Another noteworthy flaw of 24-hour urine testing in clinical practice is that these tests are rarely used for response assessments in the relapsed/refractory setting apart from specific scenarios such as AL amyloidosis. Based on our experience with later lines of therapy, physicians are much more likely to rely on biochemical progression using serum M-protein and SFLC assays or new myeloma-defining events such as lytic lesions on cross-sectional imaging. The shift away from 24-hour urine assessments in this setting is in part due to the nature of relapsed/refractory MM, but is also possible given the relative convenience of serum-based and imaging-based response assessments. This principle also applies to the newly diagnosed setting, and our work highlights that any contribution of urine testing to IMWG response assessments is likely overshadowed by the inconvenience inherent to collecting these samples.

Our study has several limitations, most importantly a modest sample size from a single institution and lack of generalizability to patients who are not being considered for ASCT. Another limitation is the 19% of screened patients ($n = 66$) who had missing data precluding any type of IMWG response assessment. These patients tended to have LC-only disease, which may have affected the accuracy of our results for this subgroup. However, this limitation also highlights the real-world challenge of accurately collecting 24-hour urine data at multiple time points. Only 29% of patients in our cohort had complete urine testing at both diagnosis and follow-up, a finding roughly in line with the 40% figure (2748 out of 6935) based on ongoing work by our group using Center for International Blood and Marrow Transplant Research (CIBMTR) data [17]. As a final limitation, we did not measure the impact of traditional versus urine-free IMWG criteria on PFS given our expectation of a small reclassification rate and thus a very small expected number of discordant responses. Validating our results with CIBMTR data and analyzing changes in PFS prognostication using urine-free criteria are active ongoing areas of research.

In conclusion, our study builds on prior research to demonstrate that 24-hour urine testing may add little

value to response assessment criteria for patients with MM who have other markers of measurable disease (and in the absence of AL amyloidosis). Further research into urine-free response criteria using larger data sets is warranted. If the removal of 24-hour urine testing is shown not to impact the prognostic impact of response criteria, steps to eliminate 24-hour urine testing for most patients – both broadly by the IMWG and individually by MM physicians – should be considered in the future. Doing so would streamline testing algorithms, lower healthcare costs, and most importantly remove the burden of an inconvenient and time-consuming test for patients.

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K.H.N., C.Y.H., and S.A. declare no competing interests. J.K. has received honoraria from Amgen and Kyprolis. A.C. has received research support from AbbVie, Bristol-Myers Squibb, CARSgen, Celgene, Caelum, Cellectis, Janssen, and Merck. A.C. has received honoraria from Sanofi. T.G.M. has consulted for GlaxoSmithKline, Juno, and Roche. T.G.M. has received research support from Amgen, Janssen, Sanofi, and Seattle Genetics. J.W. has consulted for Amgen, Celgene, Janssen, Novartis, and Takeda. S.W.W. has consulted for Amgen and Sanofi. S.W.W. has received research support from Bristol-Myers Squibb, Caelum, Genentech, Fortis, GlaxoSmithKline, and Janssen. N.S. is employed by AstraZeneca. N.S. has consulted for Amgen, Bristol-Myers Squibb, Celgene, CareDx, GlaxoSmithKline, Indapta Therapeutics, Karyopharm, Kite, and Sanofi. N.S. has received research support from Bluebird Bio, Bristol-Myers Squibb, Celgene, Janssen, Nektar, Poseida, Sutro Biopharma, and Tenebio. R.B. has consulted for Bristol Myers Squibb, Genentech/Roche, Janssen Oncology, Sanofi Pasteur, and SparkCures. R.B. has received research support from Pack Health.

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ORCID

Kelsey H. Natsuhara http://orcid.org/0000-0002-7352-7028
Rahul Banerjee http://orcid.org/0000-0003-3781-5441

Data availability statement

The data analyzed during the current study are not publicly available due to patient-identifying information but are available from the corresponding author on reasonable request.

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