Replacing Urine Protein Electrophoresis With Serum Free Light Chain Analysis as a First-Line Test for Detecting Plasma Cell Disorders Offers Increased Diagnostic Accuracy and Potential Health Benefit to Patients

Malcolm P. McTaggart, PhD,1 Jindriska Lindsay, FRCPath,2 and Edward M. Kearney, FRCPath1

From Clinical Biochemistry1 and Clinical Haematology,2 Department of Laboratory Medicine, East Kent Hospitals University NHS Foundation Trust, Canterbury, Kent, England.

Key Words: Serum free light chains; Multiple myeloma; Plasma cell disorders; Monoclonal proteins

DOI: 10.1309/AJCP25IHYLEWCAHJ

ABSTRACT

Objectives: To determine the most clinically effective diagnostic testing strategy for plasma cell disorders in the clinical laboratory.

Methods: Serum and urine samples from 2,799 patients with suspected plasma cell dyscrasias were tested by alternative diagnostic testing strategies consisting of serum protein electrophoresis (SPE) with either urine protein electrophoresis (UPE) or serum free light chain (sFLC) analysis.

Results: The combination of sFLC analysis and SPE had the greatest sensitivity (100%), detecting abnormalities in all 124 patients diagnosed with plasma cell disorders. Routine sFLC testing would have had much potential health benefit for two patients in the study population. First, a patient who had a markedly abnormal sFLC result was diagnosed with light chain deposition disease by renal biopsy, but no abnormality was detected by SPE or UPE. Second, a patient diagnosed with multiple plasmacytomas following biopsy of a lung tumor had a grossly abnormal sFLC result but an equivocal weak-positive SPE result, and no urine sample was received by the laboratory for the patient.

Conclusions: Our study suggests that the combination of SPE and sFLC analysis is the most clinically effective first-line diagnostic testing strategy for detecting plasma cell disorders in the clinical laboratory.

Multiple myeloma (MM) is a malignant disease of bone marrow plasma cells that has an annual incidence of 5.6 cases per 100,000 people in the Western world. The diagnosis of MM and related plasma cell disorders often takes longer than is desirable following first presentation to primary care; therefore, there is a need to improve the testing strategy for these diseases.

The detection and quantification of monoclonal proteins (M-proteins) is central to the diagnosis and monitoring of MM. In addition to MM, M-proteins may be present in other B-cell neoplasms, such as monoclonal gammopathy of undetermined significance (MGUS), amyloid light chain (AL) amyloidosis, plasmacytomas, leukemias, and lymphomas. Rather than conferring a specific diagnosis, the detection of M-proteins is an indication for further investigation.

To detect intact M-proteins, many researchers use serum protein electrophoresis (SPE), followed by serum immunofixation electrophoresis if an abnormality is detected. This is universally accepted as the most effective approach for detecting intact M-proteins in the clinical laboratory. However, SPE is inadequate for the detection of light chain, oligosecretory, and nonsecretory MM, as well as other plasma cell disorders (eg, AL amyloidosis and light chain deposition disease).

There has been much debate in recent years as to the most effective method for detecting monoclonal free light chains (FLCs), which are present in approximately 80% of patients with MM and are the only detectable M-protein in 20% of those with the disease. Traditionally, urine protein electrophoresis (UPE) has been used to detect FLCs in...
urine, termed *Bence-Jones protein* (BJP). The sensitivity of this method is limited due to reabsorption of FLCs in the renal tubules, meaning FLCs may not reach the urine until loss of tubular function has occurred. There are also well-recognized practical problems with getting urine samples sent to the laboratory for patients being tested for plasma cell disorders: compliance for urine accompanying the serum sample in this setting has ranged from 5% to 40% in different studies.

Most studies have found that sFLC testing has superior diagnostic sensitivity to UPE for detecting plasma cell dyscrasias, particularly AL amyloidosis, light chain deposition disease, and nonsecretory MM. However, the modestly high false-positive rate and variable analytical performance of sFLC testing have been highlighted in the literature, particularly the reported high coefficients of variation of the assays. Nevertheless, International Myeloma Working Group guidelines now recommend use of the sFLC assays as a first-line test for MM and related plasma cell disorders. United Kingdom clinical guidelines advocate use of the sFLC assays only once a monoclonal protein has been identified, as well as for detection and monitoring of nonsecretory MM and AL amyloidosis.

Previous studies have assessed the diagnostic accuracy of sFLC testing, but there has been limited analysis of their clinical utility, which is the most important consideration when evaluating a diagnostic test. The aim of this prospective study was to determine the relative clinical benefit of a first-line testing strategy of SPE and sFLC compared with that of SPE and UPE analysis.

**Materials and Methods**

Patients were eligible for inclusion in the study if their serum sample had been sent to the clinical immunology laboratory at the William Harvey Hospital (Ashford, Kent, England) as part of routine investigation for a suspected plasma cell dyscrasia. This laboratory performs all of the SPE and UPE for primary and secondary care in the East Kent area, which serves a population of approximately 759,000 people. Available serum samples received between February 1, 2011, and July 7, 2011, from eligible patients were included in the study (n = 2,799). The study was approved by the chair of the local research ethics committee.

**Index Tests**

SPE and sFLC testing was performed on all of these samples; UPE was performed when an acceptable paired urine sample (in a container without preservatives and clearly labeled with correct demographic details according to local clinical governance standards) was received by the laboratory within 30 days of the serum sample. If no such urine sample was received by the laboratory, index test results for that patient were excluded from diagnostic accuracy calculations involving UPE. SPE (protein stain only) and UPE (protein stain and bivalent immunofixation for κ and λ light chains) were carried out using a Sebia Hydragel β1-β2 kit on a semiautomated Hydrasys analyzer according to the manufacturer’s instructions (Sebia, Issy-les-Moulineaux, France) as part of the routine work of the clinical laboratory. If no protein was visible following UPE, the sample was concentrated by ultrafiltration using a BJP Clinical Concentrator device (Generon, Berkshire, England) and the UPE repeated with the concentrated sample; if there was still no protein visible in the concentrated sample, a report was sent to the requesting clinician asking for an early morning urine sample from the patient.

The sFLC testing was performed using Freelite immunoturbidimetric assays for κ and λ light chains on a SpaPlus analyzer (The Binding Site Group Ltd, Birmingham, England) with automatic calculation of the κ/λ ratio. The sFLC results were scored as positive if the κ/λ ratio was outside the published diagnostic reference range of 0.26 to 1.65. An alternative reference range of 0.37 to 3.1 was used for patients on dialysis and those who had an estimated glomerular filtration rate of less than 15 mL/min/1.73 m².

**Reference Standard**

Samples with abnormal SPE, UPE, or sFLC results were analyzed by immunofixation electrophoresis using a Sebia Hydragel 2/4 IF kit on a Hydrasys analyzer (Sebia). Diagnosis by a clinical hematologist, using local protocol based on national clinical guidelines, was the reference standard in the study. Diagnostic accuracy estimates and 95% confidence interval limits were calculated using standard formulas.

**Results**

**Study Population**

The study population consisted of 2,799 patients with a median age of 66 years (interquartile range, 26 years), 1,683 (60.1%) of whom were female. Of the 124 patients (4.4% of study population) with plasma cell disorders, 17 had malignant disease (0.6% of study population). Acceptable paired urine samples were received for 579 (20.7%) of the patients in the study cohort.
Diagnostic Accuracy of the Index Tests

Of the individual index tests, SPE had the least number (n = 7) of false-negative results. The highest clinical sensitivity (94.4%) and good specificity (97.9%) for detecting plasma cell disorders. The sFLC assays had poor sensitivity (46.8%) for detecting plasma cell disorders but good specificity (98.9%).

Diagnostic Accuracy of Different First-Line Testing Strategies

When considering different first-line diagnostic testing strategies involving two index tests, the combination of SPE and sFLC testing had the highest sensitivity (100.0%) and excellent specificity (96.9%). Used together, SPE and UPE had good sensitivity (96.1%) and specificity (95.2%) but lower than the corresponding values for the combination of SPE and sFLC. UPE used together with sFLC testing had the best specificity (97.8%) but poor sensitivity (59.7%).

A first-line testing strategy incorporating all three index tests did not improve the sensitivity compared with using just SPE and sFLC testing, while the specificity of using all three index tests was lower (94.0%) than for any two tests in combination (Table 2).

Clinical Utility of Different First-Line Diagnostic Testing Strategies

All cases of plasma cell disorders in the study population were detected by a diagnostic testing strategy of SPE and sFLC analysis. However, in three of these six patients, there was discordance between the clonality recognized by serum free light chain testing and serum immunofixation. In each of these cases, the light chain concentration was very close to the detection limit of immunofixation, and intact immunoglobulin MGUS was identified, which was missed by SPE.

Of the 17 patients diagnosed with plasma cell dyscrasias (Table 3), all had an abnormal sFLC result, 16 had an abnormal SPE result, but BJP was detected in urine samples from only 11 of these patients. Of particular relevance was a patient diagnosed with multiple plasmacytomas; only a small paraprotein was detected by SPE (<2 g/L), but the patient’s

Table 2

<table>
<thead>
<tr>
<th>Diagnostic Accuracy of the Individual Index Tests and Different Diagnostic Testing Strategies for Detecting Plasma Cell Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statistical Parameter</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Sensitivity, %</td>
</tr>
<tr>
<td>Specificity, %</td>
</tr>
<tr>
<td>PPV, %</td>
</tr>
<tr>
<td>FPR, %</td>
</tr>
<tr>
<td>NPV, %</td>
</tr>
<tr>
<td>FNR, %</td>
</tr>
<tr>
<td>LR+, %</td>
</tr>
<tr>
<td>LR–, %</td>
</tr>
</tbody>
</table>

sFLC, serum free light chains; SPE, serum protein electrophoresis; UPE, urine protein electrophoresis.

* The 95% confidence interval limits are shown in parentheses. Percentages and LR+s are given correct to one decimal place and LR–s correct to two decimal places.
Figure 1: Study flow diagram showing alternative diagnostic testing strategies for detection of plasma cell disorders in the clinical laboratory. The case of plasmacytoma is in italics for the SPE/UPE testing strategy because although SPE gave a weak positive result, it did not reflect the patient's malignant disease. LCDD, light chain deposition disease; MGUS, monoclonal gammopathy of undetermined significance; sFLC, serum free light chains; SPE, serum protein electrophoresis; UPE, urine protein electrophoresis.

Table 3: Index Test Results for Patients Diagnosed With Plasma Cell Dyscrasiasa

<table>
<thead>
<tr>
<th>sFLC Analysis</th>
<th>Patient Age, y/Sex</th>
<th>κ, mg/L</th>
<th>λ, mg/L</th>
<th>κ/λ (0.26-1.65)</th>
<th>SPE</th>
<th>Serum Immunofixation</th>
<th>UPE</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>26/F</td>
<td>331.0</td>
<td>13.0</td>
<td>25.46</td>
<td></td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>LCDD</td>
</tr>
<tr>
<td>80/F</td>
<td>14.3</td>
<td>1652.0</td>
<td>0.01</td>
<td>M-protein (&lt;2 g/L)</td>
<td>IgG λ</td>
<td>No sample</td>
<td>Multiple plasmacytomas</td>
<td></td>
</tr>
<tr>
<td>65/M</td>
<td>29.5</td>
<td>132.2</td>
<td>0.22</td>
<td>M-protein (&lt;8 g/L)</td>
<td>IgG λ</td>
<td>Negative</td>
<td>Amyloidosis</td>
<td></td>
</tr>
<tr>
<td>69/M</td>
<td>77.7</td>
<td>77.7</td>
<td>77.70</td>
<td>M-protein (40 g/L)</td>
<td>IgG κ</td>
<td>Negative</td>
<td>Symptomatic MM</td>
<td></td>
</tr>
<tr>
<td>70/F</td>
<td>23.8</td>
<td>13.1</td>
<td>1.82</td>
<td>M-protein (29 g/L)</td>
<td>IgG κ</td>
<td>Negative</td>
<td>Smoldering MM</td>
<td></td>
</tr>
<tr>
<td>89/F</td>
<td>62.5</td>
<td>1.3</td>
<td>48.08</td>
<td>M-protein (62 g/L)</td>
<td>IgG κ</td>
<td>Negative</td>
<td>Smoldering MM</td>
<td></td>
</tr>
<tr>
<td>61/M</td>
<td>128.8</td>
<td>1.4</td>
<td>92.00</td>
<td>M-protein (19 g/L)</td>
<td>IgA κ</td>
<td>k BJP</td>
<td>Symptomatic MM</td>
<td></td>
</tr>
<tr>
<td>59/F</td>
<td>20,275.0</td>
<td>10.5</td>
<td>1,931.00</td>
<td>M-protein (8 g/L)</td>
<td>IgG κ and λ, FLC</td>
<td>k BJP</td>
<td>Symptomatic MM</td>
<td></td>
</tr>
<tr>
<td>78/F</td>
<td>723.1</td>
<td>0.6</td>
<td>1,205.17</td>
<td>Condensation</td>
<td>IgA κ</td>
<td>k BJP</td>
<td>NSMM</td>
<td></td>
</tr>
<tr>
<td>79/F</td>
<td>23,819.0</td>
<td>1.3</td>
<td>18,322.31</td>
<td>M-proteinb</td>
<td>κ FLC</td>
<td>k BJP</td>
<td>Symptomatic LCMM</td>
<td></td>
</tr>
<tr>
<td>86/M</td>
<td>67.4</td>
<td>10.5</td>
<td>6.42</td>
<td>M-protein (12 g/L)</td>
<td>IgA κ</td>
<td>k BJP</td>
<td>Smoldering MM</td>
<td></td>
</tr>
<tr>
<td>68/M</td>
<td>14.1</td>
<td>8.1</td>
<td>1.74</td>
<td>M-protein (28 g/L)</td>
<td>IgG κ</td>
<td>k BJP</td>
<td>Symptomatic MM</td>
<td></td>
</tr>
<tr>
<td>59/F</td>
<td>1.1</td>
<td>279.0</td>
<td>0.00</td>
<td>M-protein (22 g/L)</td>
<td>IgG λ</td>
<td>k BJP</td>
<td>Smoldering MM</td>
<td></td>
</tr>
<tr>
<td>84/M</td>
<td>13.8</td>
<td>5.6</td>
<td>2.46</td>
<td>M-protein (26 g/L)</td>
<td>IgG κ</td>
<td>k BJP</td>
<td>Smoldering MM</td>
<td></td>
</tr>
<tr>
<td>69/M</td>
<td>280.4</td>
<td>8.5</td>
<td>32.99</td>
<td>M-protein (60 g/L)</td>
<td>IgG κ</td>
<td>k BJP</td>
<td>Symptomatic MM</td>
<td></td>
</tr>
<tr>
<td>86/F</td>
<td>25,570.0</td>
<td>1.1</td>
<td>23,245.45</td>
<td>M-proteinb</td>
<td>κ FLC</td>
<td>k BJP</td>
<td>Symptomatic LCMM</td>
<td></td>
</tr>
<tr>
<td>82/M</td>
<td>47.2</td>
<td>6.2</td>
<td>0.22</td>
<td>γ-Globulins reduced</td>
<td>Negative</td>
<td>Negative</td>
<td>λ, BJP</td>
<td>Amyloidosis</td>
</tr>
</tbody>
</table>

BJP, Bence-Jones protein; FLC, free light chain; IgA, immunoglobulin A; IgG, immunoglobulin G; LCDD, light chain deposition disease; LCMM, light chain multiple myeloma; M-protein, monoclonal protein; MM, multiple myeloma; NSMM, nonsecretory multiple myeloma; sFLC, serum free light chains; SPE, serum protein electrophoresis; UPE, urine protein electrophoresis.

a Reference ranges for sFLC results are in parentheses.
b M-protein was not quantified since it was light chain only.

dTable 4: Patients With MGUS for Whom the sFLC Ratio Was the Only Abnormal Index Test Result

<table>
<thead>
<tr>
<th>sFLC Analysis</th>
<th>Patient Age, y/Sex</th>
<th>κ, mg/L</th>
<th>λ, mg/L</th>
<th>κ/λ (0.26-1.65)</th>
<th>SPE</th>
<th>UPE</th>
<th>Serum Immunofixation</th>
</tr>
</thead>
<tbody>
<tr>
<td>90/M</td>
<td>38.8</td>
<td>12.0</td>
<td>3.23</td>
<td></td>
<td>Negative</td>
<td>No sample</td>
<td>IgA κ</td>
</tr>
<tr>
<td>55/F</td>
<td>11.2</td>
<td>6.5</td>
<td>1.72</td>
<td></td>
<td>Negative</td>
<td>No sample</td>
<td>IgG λ</td>
</tr>
<tr>
<td>75/M</td>
<td>37.3</td>
<td>16.0</td>
<td>2.33</td>
<td></td>
<td>Negative</td>
<td>No sample</td>
<td>IgA κ</td>
</tr>
<tr>
<td>66/M</td>
<td>264.3</td>
<td>5.2</td>
<td>50.83</td>
<td></td>
<td>Negative</td>
<td>No sample</td>
<td>IgA κ</td>
</tr>
<tr>
<td>67/F</td>
<td>1.0</td>
<td>8.7</td>
<td>0.11</td>
<td></td>
<td>Negative</td>
<td>Negative</td>
<td>IgG κ</td>
</tr>
<tr>
<td>77/M</td>
<td>39.3</td>
<td>16.2</td>
<td>2.37</td>
<td></td>
<td>Negative</td>
<td>Negative</td>
<td>IgM λ</td>
</tr>
</tbody>
</table>

IgA, immunoglobulin A; IgG, immunoglobulin G; MGUS, monoclonal gammopathy of undetermined significance; sFLC, serum free light chains; SPE, serum protein electrophoresis; UPE, urine protein electrophoresis.

a Text is italicized for patients for whom the opposite type of paraprotein was detected by serum immunofixation than was expected based on the sFLC ratio.
sFLC result was grossly abnormal (κ = 14.27, λ = 1,652, and κ/λ = 0.01) and reflected the malignant disease present. No urine sample was received for the patient despite requests on reports issued by the clinical laboratory.

**Discussion**

A recent review by the Agency for Healthcare Research and Quality in the United States concluded there was insufficient evidence to recommend that sFLC analysis should replace UPE as a first-line test for plasma cell disorders, mainly due to limited prospective studies assessing sFLC analysis in this context. Therefore, the prospective study we present here is particularly relevant to the debate on whether sFLC testing should replace UPE. To our knowledge, our study population is larger than any previously published assessing the diagnostic accuracy of sFLC, UPE, and SPE testing in the detection of plasma cell disorders. Furthermore, we have considered the relative clinical utility of these tests by examining individual cases within the study population where index test results were discrepant.

Since the aim of our study was to determine the most effective first-line testing strategy for plasma cell disorders, the important diagnostic accuracy estimates to consider are sensitivity, likelihood ratio negative, negative predictive value, and false-negative rate. SPE performed best by these parameters with by far the greatest sensitivity (94.4%) of the individual index tests for detecting plasma cell disorders. The addition of sFLC testing alongside SPE gave an increase in sensitivity (to 100.0%), while the addition of UPE gave a smaller increase in sensitivity (to 96.1%). Furthermore, adding UPE to the combination of SPE and sFLC testing actually decreased the specificity, since UPE gave four false-positive results (ie, there was a detectable band by urine but not serum immunofixation). This finding has been termed *idiopathic Bence-Jones proteinuria* and has a favorable prognosis. In contrast, an abnormal sFLC ratio has been shown to indicate a poor prognosis for patients with MGUS. The use of sFLC testing together with UPE was insensitive to be used as a first-line diagnostic testing strategy. This is unsurprising since SPE primarily identifies intact M-proteins, while the main role of UPE and sFLC testing is to detect FLCs. Therefore, the choice is between UPE and sFLC analysis, with SPE indispensable in the detection of plasma cell disorders.

It is becoming increasingly recognized that determining only the diagnostic accuracy of laboratory tests is insufficient and that assessing their clinical utility is paramount. In our study, there was one case of malignant disease in which sFLC analysis gave the only abnormal index test result for a further six patients who were not diagnosed with a plasma cell dyscrasia but for whom an M-protein was detected by serum immunofixation (ie, they had MGUS). These M-proteins were so minor that they were not seen by SPE due to comigration with other serum proteins. The light chain type of three of these M-proteins was actually opposite to that inferred by the sFLC ratio (ie, λ containing paraprotein when κ would be expected based on the sFLC ratio and vice versa). Given the relatively low immunoglobulin light chain concentrations in the serum samples from these patients, the identification of MGUS is difficult to establish as the concentrations are close to the limit of the analytical sensitivity of both the sFLC assays and immunofixation. In addition, due to the renal clearance of immunoglobulin light chains, sFLC ratios close to the edge of the reference range need to be interpreted in light of the patient’s kidney function to determine if the sFLC result is likely to be due to reduced renal clearance or B-cell disease. There is currently no algorithm for adjusting the sFLC ratio for kidney function, meaning that interpretation of borderline sFLC results in the context of mild renal impairment relies on a combination of clinical and analytical expertise.

Clinically, there would have been clear benefit in using sFLC analysis as part of routine diagnostic testing for the patient with light chain deposition disease. This patient was found to have renal impairment following a primary care consultation and was subsequently referred to a nephrologist. The diagnosis of light chain deposition disease was made by renal biopsy 3 weeks after the index SPE. If the sFLC assays had been in routine use, the diagnosis could have been made much earlier, or at least the result would have confirmed the suspicion that a plasma cell dyscrasia was the cause of the patient’s renal disease. Although the patient does not currently require renal replacement therapy, a quicker diagnosis with the aid of sFLC testing could have allowed earlier initiation of treatment, which can make a significant difference when preventing renal failure.

The use of sFLC testing would also have potentially offered much benefit to the patient diagnosed with multiple plasmacytomas. This patient had a history of equivocal SPE results: in 2003, SPE showed a slight irregularity that was not conclusive, and a subsequent sample was analyzed 6 months later with no abnormality detected. During the following 8 years, the patient had a number of primary care and outpatient appointments, as well as inpatient stays, some of which were potentially attributable to plasma cell dyscrasias, including a fractured neck of the femur and recurrent infections. In 2011, a third SPE was performed and a minor band was detected and typed by immunofixation (immunoglobulin G λ, <2 g/L). The patient’s index sFLC result was grossly abnormal, suggesting some form of plasma cell dyscrasia; a diagnosis of multiple plasmacytomas was subsequently
made following biopsy of a lung tumor. The patient has since died; at the time of diagnosis, the patient’s performance status was too poor to consider any systemic treatment. Assessing the impact of sFLC testing 8 years hence is conjecture; however, the results of a large study in which sFLC analysis was performed on archived serum samples from patients who developed MM strongly suggested that an abnormal sFLC ratio preceeds malignant transformation. Therefore, the hypothesis that the sFLC ratio would have been abnormal in this patient 8 years before diagnosis is not without merit. It is also important to note that BJP was detected in urine samples from only 11 of the 16 patients diagnosed with plasma cell dyscrasias who had an abnormality detected by SPE, whereas the sFLC ratio was abnormal in the index serum samples from all of these patients. Therefore, sFLC analysis would have been useful as a first-line test in this group of patients to confirm the abnormality detected by SPE and to help guide intervention. The relative benefits of sFLC testing and UPE to the patients with MGUS in this study would require long-term follow-up.

A further advantage of replacing UPE with sFLC testing is the provision of a sensitive diagnostic test for FLCs in all patients and not just those for whom an acceptable urine sample has been received by the laboratory. In our study, the proportion of patients for whom a paired urine sample was received (20.7%) is consistent with that seen in previous studies where urine compliance rates have ranged from 5% to 40%. This highlights the practical problems of using UPE as a first-line test, and the issue is solved by replacing UPE with sFLC analysis.

There is some concern as to the financial implications of making the change from UPE to sFLC testing. On the basis of reagent and staff costs, we have estimated the total price of UPE and sFLC to be approximately £11 ($17) and £19 ($29), respectively; therefore, the introduction of sFLC will bring an initial increase in costs to the laboratory. However, if the proportion of paired urines received with the serum sample were to increase, it would require a greater number of staff to cope with the increased workload, thus increasing costs, whereas we believe replacing UPE with sFLC would not require extra staff because it is less labor-intensive than UPE. There are two main reasons for this: first, sFLC testing is more high throughput than UPE; second, the same sample can be used for SPE and sFLC testing, whereas UPE requires a further sample to be processed, which usually requires aliquoting and often needs to be concentrated prior to analysis.

A full health economic study is really needed to address the relative cost-effectiveness of the two tests—that is, does the more sensitive detection of plasma cell disorders by sFLC testing cause significant savings due to reduced presentation of patients with end-stage disease complications? For example, the patient in our study with multiple plasmacytomas may have been diagnosed earlier, saving hospital visits due to symptoms of unknown cause (eg, pathologic fracture and infections). The caveat to this argument is the cost associated with treatment of plasma cell dyscrasias; however, this cost could be justified by the health benefits.

Imperfections of the sFLC assays have been well documented in the literature. Consistent with previous studies, we found a reasonably high false-positive rate (34.1%); one publication concluded that due to the false positives and false negatives associated with the sFLC assays, they were not suitable for replacing UPE. However, these conclusions have been questioned following consideration of the clinical context—that is, false positives are acceptable for a first-line “screening” test, and the false negatives were actually patients with idiopathic Bence-Jones proteinuria, which is not considered a true monoclonal gammopathy by international guidelines. Furthermore, in our study, the false-negative rate of UPE (8.8%) was higher than that of sFLC analysis (2.4%), demonstrating that the argument for not using sFLC testing due to its false-negative rate is incorrect.

Most studies have found that sFLC testing is superior to UPE in detecting plasma cell disorders, and some clinical laboratories have embraced this evidence and replaced UPE with the sFLC assays. However, a recent review concluded there was insufficient evidence to support the change in practice due to a lack of prospective studies addressing this question. Therefore, our finding that sFLC analysis is more clinically effective than UPE as a first-line test for plasma cell disorders is particularly relevant.

The two patients in our study who would most clearly have benefited from routine sFLC testing were identified in a period of approximately 5 months; therefore, in theory, there would be around five patients per year in East Kent gaining a major health benefit from sFLC analysis being used as a first-line test for plasma cell disorders. We also found that sFLC testing confirmed all abnormal SPE results in patients with plasma cell dyscrasias, whereas BJP was detected in urine samples from only 11 of these patients. This suggests that sFLC testing complements SPE better than does UPE, giving the clinicians useful additional information that UPE cannot always provide.

In summary, our findings are consistent with the existing evidence on the diagnostic accuracy of tests for plasma cell disorders, which have shown that sFLC testing has superior clinical sensitivity to UPE. Furthermore, our findings suggest that a first-line diagnostic testing strategy of SPE and sFLC analysis offers greater health benefit to patients than the alternative combination of SPE and UPE.

Address reprint requests to Dr McTaggart: m.mctaggart@nhs.net.
Acknowledgments: We are grateful to staff in the clinical laboratory at the William Harvey Hospital for performing the electrophoresis and immunofixation analysis as part of their routine work and also for allowing access to the samples and data required for this study. We also thank Fiona Kilvington, MSc, Ladan Adie, PhD, and Stephen Harding, PhD, The Binding Site Group Ltd, Birmingham, England, for organizing provision of reagents and for critical discussion of our data and manuscript.

References