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## Screening Panels for Detection of Monoclonal Gammopathies

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### Abstract

**BACKGROUND**—The repertoire of serologic tests for identifying a monoclonal gammopathy includes serum and urine protein electrophoresis (PEL), serum and urine immunofixation electrophoresis (IFE), and quantitative serum free light chain (FLC). Although there are several reports on the relative diagnostic contribution of these assays, none has looked at the tests singly and in combination for the various plasma cell proliferative disorders (PCPDs).

**METHODS**—Patients with a PCPD and all 5 assays performed within 30 days of diagnosis were included (n = 1877). The diagnoses were multiple myeloma (MM) (n = 467), smoldering multiple myeloma (SMM) (n = 191), monoclonal gammopathy of undetermined significance (MGUS) (n = 524), plasmacytoma (n = 29), extramedullary plasmacytoma (n = 10), Waldenström macroglobulinemia (WM) (n = 26), primary amyloidosis (AL) (n = 581), light chain deposition disease (LCDD) (n = 18), and POEMS syndrome (n = 31).

**RESULTS**—Of the 1877 patients, 26 were negative in all assays. Omitting urine from the panel lost an additional 23 patients (15 MGUS, 6 AL, 1 plasmacytoma, 1 LCDD), whereas the omission of FLC lost 30 patients (6 MM, 23 AL, and 1 LCDD). The omission of serum IFE as well as urine lost an additional 58 patients (44 MGUS, 7 POEMS, 5 AL, 1 SMM, and 1 plasmacytoma).

**CONCLUSIONS**—The major impact of using a simplified screening panel of serum PEL plus FLC rather than PEL, IFE, and FLC is an 8% reduction in sensitivity for MGUS, 23% for POEMS (7 patients), 4% for plasmacytoma (1 patient), 1% for AL, and 0.5% for SMM. There is no diminution in sensitivity for detecting MM, macroglobulinemia, and LCDD.

Because of the secreted monoclonal immunoglobulin, plasma cell proliferative disorders (PCPDs)<sup>4</sup> are generally classified among monoclonal gammopathies. These diseases include

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malignant disorders such as multiple myeloma (MM), plasmacytoma, plasma cell leukemia, and Waldenström macroglobulinemia (WM); premalignant diseases such as monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM); and protein or low tumor burden diseases such as primary amyloidosis (AL), light chain deposition disease (LCDD), and POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes). Because of the wide range of biology and disease presentations, identification of the monoclonal immunoglobulin may often be the first clue to the diagnosis. The recognition of the monoclonal protein may be trivial or may require multiple approaches. The malignant disease of MM, for example, usually presents with a significant amount of monoclonal protein, but even within this malignant diagnosis, there is a subclassification of nonsecretory MM which secretes little or no monoclonal protein.

The diagnostic screening panels for patients suspected of MM, AL, and related monoclonal gammopathies have traditionally included protein electrophoresis (PEL) and immunofixation electrophoresis (IFE) of both serum and urine (1). The recent introduction of quantitative serum assays for immunoglobulin free light chain (FLC), however, has increased the sensitivity of laboratory testing strategies for identifying monoclonal gammopathies (2, 3); this increased diagnostic sensitivity is readily apparent in the monoclonal light chain diseases (4, 5). Because of the increased sensitivity for free light chain diseases, the most recent diagnostic screening recommendations are that serum IFE plus FLC is a sufficient screening panel for PCPDs other than AL (6). It is recommended, however, that screening for AL should also include urine IFE.

Because the quantitative FLC assay is relatively new, the benefits and drawbacks of various testing strategies in the different PCPDs are not entirely clear. A number of approaches for diagnostic screens have been proposed, and these include urine PEL/IFE and serum PEL/IFE/FLC (7), serum PEL/IFE/FLC (8, 9), serum PEL/FLC (10, 11), and serum PEL and clinical history (12). Studies have focused on a specific diagnosis such as MM (4, 13) or AL (5, 7, 14); analyzed a patient subset such as patients with urinary monoclonal proteins (9); or investigated small numbers of monoclonal gammopathy patients (10, 15).

We identified a large cohort of untreated patients with an assortment of plasma cell proliferative diseases. These patients' records all contained urine PEL and IFE as well as serum PEL, IFE, and FLC within 30 days of their diagnosis. The purpose of this study was to assess the sensitivity of the various tests or combinations of tests for detecting monoclonal gammopathies in patients with PCPDs.

## Materials and Methods

We queried the dysproteinemia database for the first results of all Mayo Clinic patients with a monoclonal gammopathy who also had serum PEL, IFE, and FLC and urine PEL and IFE performed within 30 days of diagnosis. This list of 1877 patients contained the patient's diagnosis, date of diagnosis, date of laboratory tests, urine IFE and PEL results, and serum PEL, IFE, and FLC results. The requirement for all data to be within 30 days of diagnosis was to ensure that no treatment would affect the test results. The 1877 patients that fulfilled the inclusion criteria were diagnosed at Mayo Clinic between February 18, 2002, and December 23, 2008. The serum FLC assay was formally introduced into our clinical practice

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<sup>4</sup>Nonstandard abbreviations: PCPD, plasma cell proliferative disorder; MM, multiple myeloma; WM, Waldenström macroglobulinemia; MGUS, monoclonal gammopathy of undetermined significance; SMM, smoldering MM; AL, amyloidosis; LCDD, light chain deposition disease; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes; PEL, protein electrophoresis; IFE, immunofixation electrophoresis; FLC, free light chain.

in May 2002. In addition to the 1877 patients included in this study, there were 5235 Mayo Clinic PCPD patients who were diagnosed during the accrual period but who were excluded because they did not fulfill the inclusion criteria of having all 5 tests performed within 30 days of diagnosis (Table 1). All queries to the dysproteinemia database or patient medical records followed a protocol approved by the Mayo Clinic Institutional Review Board. The dysproteinemia database is a Mayo Clinic research resource supported by the NCI and contains patient demographics, abstracted clinical information, and laboratory data on all Mayo Clinic dysproteinemia patients.

The serum PEL, IFE, and FLC assays were performed on the same day as the venipuncture and were reported to the patient's medical record. The FLC assay (Freelite™, The Binding Site Ltd.) was performed on a Dade Behring BNII automated nephelometer. In addition to reporting the  $\kappa$  and  $\lambda$  FLC concentration, the assay reports the FLC  $\kappa/\lambda$  ratio (diagnostic range 0.26–1.65), and an abnormal FLC result was defined as an abnormal FLC  $\kappa/\lambda$  ratio. The serum PEL assay was performed by agarose gel electrophoresis (REP; Helena Laboratories). An abnormal serum PEL was defined by the presence of a quantifiable M-spike, fuzzy band, hypogammaglobulinemia (<5.5 g/L), increased  $\kappa$  fraction (>16 g/L), or increased  $\lambda$  fraction (>15 g/L). Some serum PEL abnormalities were not abnormal by serum IFE (e.g., hypogammaglobulinemia); they were coded as an abnormal PEL in this study if the urine or serum FLC assay was also abnormal and therefore the PEL had flagged the abnormality. The serum IFE assessed migration patterns for  $\kappa$ ,  $\lambda$ ,  $\mu$ ,  $\delta$ , and immunoglobulin chains (Hydrasys and Hydragel; Sebia). Any samples containing monoclonal light chains but no monoclonal heavy chains were also tested with  $\kappa$  and  $\lambda$  antisera.

Urine PEL and IFE assays were performed on the same day as receipt of the sample and were reported to the patient's medical record. Urine samples were concentrated to a maximum of 200 $\times$  to attempt to achieve final concentrations of urine protein between 20 and 80 g/L. Urine PEL was performed on agarose gel (REP) and urine IFE on SPIFE IFE 9/15 gels (Helena Laboratories). All serum and urine PEL and IFE gels were reviewed by 2 technicians as well as by J.A. Katzmann, A. Dispenziera, J.A. Lust, M.R. Snyder, or R.A. Kyle.

We grouped the patients into 9 disease groups (MM, SMM, MGUS, plasmacytoma, extramedullary plasmacytoma, WM, AL, LCDD, and POEMS syndrome). The MM group of 467 patients included 451 MM, 4 nonsecretory MM, 4 plasma cell leukemia, 1 osteosclerotic (non-POEMS) myeloma, and 7 indolent myelomas. The 26 macroglobulinemia patients included 18 WM, 5 smoldering WM, and 3 cryoglobulinemias. The 524 MGUS patients included 41 patients with idiopathic Bence Jones proteinuria.

## Results

The data query identified 1877 patients with a diagnosis of a monoclonal gammopathy who had urine PEL and IFE as well as serum PEL, IFE, and FLC results that were obtained within 30 days of diagnosis. These patients were grouped into 9 diagnostic categories (Table 1). During this same time interval, there were 5235 patients diagnosed with a PCPD who did not have all the assays performed within 30 days of diagnosis and were excluded from the data analysis. Only 10% of the MGUS patients are included in this study. The excluded MGUS patients (n = 4644) comprise 89% of the patients missing at least 1 of the tests within 30 days of diagnosis. Of the 5168 MGUS patients diagnosed during the accrual period, only 25% had urine studies and 16% had serum FLC quantification.

The 9 diagnostic groups are listed in Table 2, and the ability of tests and test panels to identify patients in each group is presented. The upper portion of the table lists the actual numbers of patients that are abnormal with each test panel, and the lower portion presents the data as the percent of abnormal results in each patient category.

The use of all the urine and serum tests identified 1851 patients (98.6%) as abnormal. There were 26 patients whose diagnosis was not detected with these tests: 11 with AL (1.9% of total AL); 8 with extramedullary plasmacytoma (80%); 3 with plasmacytoma (10.3%); 3 with LCDD (16.7%); and 1 with POEMS syndrome (3%).

The testing panel of urine IFE plus serum PEL and IFE (without serum FLC) missed 30 additional patients. The 30 patients included 6 MM, 23 AL, and 1 LCDD.

A testing panel of serum PEL, IFE and FLC (without urine studies) missed 23 patients in addition to those missed when using all the urine and serum tests. The 23 patients missed by omission of urine tests included 15 MGUS, 1 extramedullary myeloma, 1 LCDD, and 6 AL. The 6 AL patients all had monoclonal light chains detected in the urine. The 6 of 581 AL patients (1.0%) compares to previous studies that identified 0 of 123 (0%) (9) and 5 of 115 (4.3%) (7) AL patients in whom urine studies were required for identification of the monoclonal gammopathy.

In addition to assessing the contribution of serum FLC and urine tests in screening for these diseases, we wanted to determine the performance of serum PEL, IFE, and FLC vs serum PEL plus FLC. When serum PEL plus FLC was the testing panel, 58 patients were missed compared to a panel of serum PEL, IFE, and FLC. These 58 patients included 44 patients with MGUS, 7 with POEMS, 5 with AL, 1 with plasmacytoma, and 1 with SMM (Table 2). The use of serum PEL plus FLC compared with serum PEL, IFE, and FLC did not miss any patients with MM, macroglobulinemia, or LCDD.

Serum PEL, IFE, and FLC assays did not perform well as single tests. PEL and IFE missed patients in every disease category except macroglobulinemia, whereas FLC did not identify 100% of the patients in any category (Table 2). Among the 57 AL patients that were missed by the serum FLC assay but identified by urine and/or serum IFE, 52 (91%) expressed light chains.

## Discussion

The laboratory contribution to the diagnosis of monoclonal gammopathies has relied on serum and urine PEL and IFE and now includes quantitative serum FLC assays. It is recognized that the serum FLC assay is a sensitive additional test for monoclonal light chain diseases. In this study the addition of serum FLC captured 23 AL, 6 MM, and 1 LCDD that were not detected by the traditional panel of serum and urine tests. The incorporation of serum FLC assays into screening panels for the recognition of monoclonal gammopathies, however, has not been fully evaluated, and the benefit of various combinations of tests has not been clear. As documented in this study and in many previous publications, no single clinical laboratory test has sufficient sensitivity for the spectrum of PCPDs.

Herein, we have clearly demonstrated that different screening approaches may be effective for different plasma cell disorders (Table 3). When screening for MM or WM, a panel of serum PEL and FLC is adequate assuming that the PEL reflex algorithm is followed as described in Materials and Methods. In contrast, for suspected diagnoses of LCDD and AL, serum and urine IFE should be added to the serum FLC to maximize sensitivity. In intramedullary solitary plasmacytoma and POEMS syndrome, the FLC assay is less sensitive than serum IFE serum, and all 3 serum tests should be included when these

diagnoses are suspected. Finally, for MGUS some sensitivity is lost with a PEL and FLC screening panel, but these MGUS patients will be among patients with the lowest risk for progression to MM.

Our findings are not dissimilar to previous publications, but the current data differ in that they are more definitive due to comprehensive testing done on a variety of patients with documented plasma cell disorders. We previously reported that the use of serum PEL, IFE, and FLC as a diagnostic screen was a sensitive approach for identifying monoclonal gammopathies in a cohort of patients with abnormal urine studies (9). This led to the recommendation of omitting urine studies from the initial testing panel. Subsequent studies that focused on AL documented a 96% sensitivity for serum IFE plus FLC (7) and emphasized the need for continued use of urine assays for early intervention in AL. In the study of Palladini et al. (7), 5 of 115 AL patients were missed by serum IFE plus FLC but were identified as abnormal by urine IFE. These data (9, 7) prompted the International Myeloma Working Group to recommend that screening panels for monoclonal gammopathies should include serum PEL, IFE, and FLC and that urine studies should be added for diagnosing AL (6). Our current series confirms these recommendations for urine. We report 581 AL patients; 11 of these patients (1.9%) had no detectable abnormality in any of our serum and urine assays. Among 570 patients with a detectable monoclonal protein, 6 patients (1.0%) would have been missed if urine was omitted from the screening panel. As in Palladini's report, the AL patients who had abnormal urine studies and normal serum FLC all had monoclonal light chains, suggesting a gap in the FLC antiserum.

Laboratories that perform serum PEL as the initial diagnostic testing for monoclonal gammopathies have considered the addition of quantitative FLC as a way to increase sensitivity and constrain the costs of diagnostic testing. Bakshi et al. (10) performed capillary zone electrophoresis on 1003 consecutive samples, identified 39 patients with monoclonal gammopathies, and found that the addition of the FLC assay identified an additional 16 patients. They did not, however, perform IFE to define the total number of cases. Our current series tests the sensitivity of this approach. The combination of PEL plus FLC had the same sensitivity as PEL, IFE, and FLC for MM, WM, and LCDD, but missed a large number of patients with MGUS ( $n = 42$ ) and a high percentage of POEMS (23%), along with 5 AL, 1 plasmacytoma, and 1 SMM. MGUS is an asymptomatic premalignant disorder with a prevalence of 3% in the population older than 50 years (16). Population-based screening to identify MGUS is not recommended, but because MGUS progresses to MM at a rate of 1% per year (17), patients should be monitored for progression once they have been identified. The 44 MGUS patients that were missed by using a screening panel of PEL plus FLC are among the lowest risk for progression. Low risk factors for progression to MM include a serum M-spike  $<15$  g/L and a normal serum FLC / ratio (18): patients with the lowest risk for progression have a 2% 20-year risk of developing MM. The consequence of missing these low-risk MGUS patients should not be severe. Because 98% of these patients will likely never develop MM, the savings in periodic testing and patient anxiety may actually be beneficial.

The insensitivity of all of the serum assays used in isolation is a reminder that serum PEL and/or IFE should be used in combination with either urine IFE and/or serum FLC. Urine IFE and quantitative serum FLC assays both detect small numbers of abnormalities that the other may miss (5, 7, 8, 14, 15, 19, 20). In this current study, the urine assay in combination with serum IFE detected 15 MGUS, 6 AL, 1 LCDD, and 1 extramedullary plasmacytoma that were missed by the serum FLC assay in combination with serum IFE. Conversely, the serum FLC assay in combination with serum IFE detected 6 MM, 23 AL, and 1 LCDD that were missed by the urine assay in combination with serum IFE.



The Mayo Clinic is a primary practice as well as a referral practice. Although our data on disease sensitivity is applicable to other practices, disease specificity depends on the distribution of patients that have screening panels ordered. An early publication on the use of the serum FLC assay when ordered from a hematology practice documented 100% specificity (8). Subsequent studies evaluating general hospital and outpatient populations documented specificities of 96%–98.5% (10, 11, 20). A majority of the false-positive FLC results exhibit slightly increased FLC /  $\kappa$  ratios (1.65–3), and a high percentage of these fall in the newly defined chronic kidney disease reference range (21). As renal clearance significantly declines, there is no longer a preferential removal of  $\lambda$  FLC from the blood, and the FLC /  $\kappa$  ratio rises to reflect the total light chain /  $\kappa$  ratio. These false-positive results have led to some wariness about the use of the serum FLC assay in screening panels. The FLC specificity, however, can be compared to the specificity of serum PEL, which has been the backbone of screening for many decades. In this study, we defined the PEL as abnormal if there was a quantifiable M-spike, a fuzzy restricted-migration band, hypogammaglobulinemia, or increased  $\lambda$  or  $\kappa$  fractions. Using these criteria, the PEL specificity is 92.5%. No large studies evaluating various screening panels have been done, and the specificity of the PEL and FLC testing panel is unknown.

Serum IFE, PEL, and FLC combined with urine IFE and PEL is the most comprehensive and inclusive panel to screen for monoclonal gammopathies. However, because of the small incremental sensitivity provided by urine studies and serum IFE, the use of serum PEL plus FLC provides a simple and efficient initial diagnostic screen for the high-tumor-burden monoclonal gammopathies such as MM, WM, and SMM. Urine studies and serum IFE can be ordered more selectively.

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**Table 1**

Mayo Clinic plasma cell proliferative disorders, February 18, 2002, through December 23, 2008.

Diagnosis	Total cases	Included, n (%)	Excluded, n (%)
All	7112	1877 (26)	5235 (74)
MM	684	467 (68)	217 (32)
WM	101	26 (26)	75 (74)
SMM	277	191 (70)	86 (31)
MGUS	5168	524 (10)	4644 (90)
Plasmacytoma	47	26 (55)	21 (45)
POEMS	43	31 (72)	12 (28)
Extramedullary plasmacytoma	19	10 (53)	9 (47)
AL	747	581 (78)	166 (22)
LCDD	23	18 (78)	5 (22)



**Table 2**

Sensitivity of monoclonal gammopathy screening panels.

Diagnosis, n	n	All 5 tests	Serum PEL and IFE; urine IFE	Serum PEL, IFE, and FLC	Serum PEL and FLC	Serum IFE	Serum PEL	Serum FLC
All	1877	1851	1821	1828	1770	1632	1482	1395
MM	467	467	461	467	467	441	409	452
Macroglobulinemia	26	26	26	26	26	26	26	19
SMM	191	191	191	191	190	188	180	155
MGUS	524	524	524	509	465	486	429	222
Plasmacytoma	29	26	26	26	25	21	21	16
POEMS	31	30	30	30	23	30	23	3
Extramedullary plasmacytoma	10	2	2	1	1	1	1	1
Primary AL	581	570	547	564	559	429	383	513
LCDD	18	15	14	14	14	10	10	14
Diagnosis, %								
All	98.6	97.0	97.4	94.3	87.0	79.0	74.3	
MM	100.0	98.7	100.0	100.0	94.4	87.6	96.8	
Macroglobulinemia	100.0	100.0	100.0	100.0	100.0	100.0	73.1	
SMM	100.0	100.0	100.0	99.5	98.4	94.2	81.2	
MGUS	100.0	100.0	97.1	88.7	92.8	81.9	42.4	
Plasmacytoma	89.7	89.7	89.7	86.2	72.4	72.4	55.2	
POEMS	96.8	96.8	96.8	74.2	96.8	74.2	9.7	
Extramedullary plasmacytoma	20.0	20.0	10.0	10.0	10.0	10.0	10.0	
Primary AL	98.1	94.2	97.1	96.2	73.8	65.9	88.3	
LCDD	83.3	77.8	77.8	77.8	55.6	55.6	77.8	

**Table 3**

Screening panels for different plasma cell disorders.

	Serum PEL	Serum FLC	Serum IFE	Urine PEL/IFE
MM	Yes	Yes		
WM	Yes	Yes		
SMM	Yes	Yes		
MGUS	Yes	Yes		
Plasmacytoma	Yes	Yes	Yes	
POEMS	Yes	Yes	Yes	
AL	Yes	Yes	Yes	Yes
LCDD	Yes	Yes	Yes	Yes