

Table 1. Coprevalence of human IgG reactive with cTnI and cTnT in serum or plasma from normal blood donors.

	Group 1 (α -cTnI ⁺ / α -cTnT ⁻) ^a	Group 2 (α -cTnI ⁻ / α -cTnT ⁺)	Group 3 (α -cTnI ⁺ / α -cTnT ⁺)	Group 4 (α -cTnI ⁻ / α -cTnT ⁻)
n	27	22	6	290
Average age, years (range)	44 (20–64)	37 (19–57)	36 (20–55)	38 (18–72)
Sex ratio, M:F	4.2	1.0	4.0	1.0
Median S/LC _{α-cTnI} (range)	10.9 (7.1–95.6)	1.2 (0.5–6.7)	15.3 (7.5–41.6)	1.3 (0.1–6.7)
Median S/LC _{α-cTnT} (range)	2.0 (0.5–4.5)	8.9 (5.4–31.4)	9.3 (6.8–44.7)	1.2 (0.1–5.1)

^a α -cTnI⁺ was defined as S/LC > 6.7; α -cTnT⁺ was defined as S/LC > 5.3.

itive based on the previously reported criteria of S/LC _{α -cTnI} > 6.7 or S/LC _{α -cTnT} > 5.3 (1, 2). Taken together, 55 (15.9%) of the 345 samples were positive for autoantibodies to cardiac troponin I or T isoforms. In these positive samples, 10.9% (6 of 55) were positive for both autoantibodies. The odds of being positive for both autoantibodies increased in the presence of either species; in samples positive for autoantibodies to cTnI, the coprevalence of α -cTnT was 18.1% (6 of 33), and in α -cTnT-positive samples, the coprevalence of α -cTnI was 21.4% (6 of 28).

The high coprevalence of autoantibodies to cTnT with autoantibodies to cTnI warrants caution in interpreting the significance of a negative or positive cTnT value that contradicts that of cTnI, and vice versa. One should consider that an autoantibody to antigen may have a negative (interference) or positive (stabilizing) effect on the measurement of the antigen, and that multiple autoantibody/antigen pairs may act independently.

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Screening Panels for Detection of Monoclonal Gammopathies: Confidence Intervals

To the Editor:

The recent article in *Clinical Chemistry* by Katzmman et al. (1) on screening panels to detect monoclonal gammopathies provided important information on the use of the free light chain (FLC)¹ assay, and we commend the authors for this report. Apart from the selection bias inherent in the exclusion of 90% of cases of monoclonal gammopathy of uncertain significance (MGUS), we would like to address some aspects that, in our opinion, may enhance understanding of the role of various diagnostic strategies to detect mono-

¹ Nonstandard abbreviations: FLC, free light chains; MGUS, monoclonal gammopathy of uncertain significance; IFE, immunofixation electrophoresis; PEL, protein electrophoresis.

Table 1. Sensitivity of monoclonal gammopathy screening panels.^a

	All 5 tests	Serum PEL, IFE, and uIFE ^b	Serum PEL, IFE, and FLC	Serum PEL and FLC	Serum IFE	Serum PEL	Serum FLC
All	98.6 (98.1–99.2)	97.0 (96.2–97.8)	97.4 (96.7–98.1)	94.3 (93.2–95.4)	87.0 (85.5–88.5)	79.0 (77.2–80.8)	74.3 (72.3–76.3)
MM	100.0 (99.4–100.0)	98.7 (97.5–99.9)	100.0 (99.4–100.0)	100.0 (99.4–100.0)	94.4 (92.3–96.5)	87.6 (84.6–90.6)	96.8 (95.1–98.5)
Macroglobulinemia	100.0 (91.1–100.0)	100.0 (91.1–100.0)	100.0 (91.1–100.0)	100.0 (91.1–100.0)	100.0 (91.1–100.0)	100.0 (91.1–100.0)	73.1 (56.7–89.5)
SMM	100.0 (98.6–100.0)	100.0 (98.6–100.0)	100.0 (98.6–100.0)	99.5 (97.8–100.0)	98.4 (96.2–100.0)	94.2 (90.7–97.7)	81.2 (75.6–86.8)
MGUS	100.0 (99.5–100.0)	100.0 (99.5–100.0)	97.1 (95.6–98.6)	88.7 (86.0–91.4)	92.8 (90.5–95.1)	81.9 (78.6–85.2)	42.2 (38.0–46.4)
Plasmacytoma	89.7 (77.5–100.0)	89.7 (77.5–100.0)	89.7 (77.5–100.0)	86.2 (73.0–99.4)	72.4 (56.7–88.1)	72.4 (56.7–88.1)	55.2 (38.2–72.2)
POEMS	96.8 (87.5–100)	96.8 (87.5–100)	96.8 (87.5–100)	74.2 (57.4–89.2)	96.8 (87.5–100)	74.2 (57.4–89.2)	9.7 (0.0–21.3)
Extramedullary plasmacytoma	20.0 (0.0–43.7)	20.0 (0.0–43.7)	10.0 (0.0–31.5)	10.0 (0.0–31.5)	10.0 (0.0–31.5)	10.0 (0.0–31.5)	10.0 (0.0–31.5)
Primary amyloidosis	98.1 (96.9–99.3)	94.2 (92.3–96.15)	97.1 (95.7–98.5)	96.2 (94.6–97.8)	73.8 (70.2–77.4)	65.9 (62.1–69.7)	88.3 (85.7–90.9)
LCDD	83.3 (65.8–100.0)	77.8 (59.2–96.4)	77.8 (59.2–96.4)	77.8 (59.2–96.4)	55.6 (34.8–76.4)	55.6 (34.8–76.4)	77.8 (59.2–96.4)

^a Adapted, with permission, from Katzmman et al. (1). Results are presented as % (95% CI), calculated with the modified Wald method [Motulsky (2)].
^b uIFE, urine IFE; MM, multiple myeloma; SMM, smoldering MM; POEMS, polyneuropathy organomegaly endocrinopathy monoclonal gammopathy and skin changes syndrome; LCDD, light chain deposition disease.

clonal gammopathies in routine laboratories.

Katzmann and coworkers did not make any statement regarding the statistical significance of their findings, nor did they provide CIs of the percentages in their Table 2. In deciding whether a particular diagnostic strategy is worthwhile to implement, it is useful to know whether any observed differences can be explained by chance; to do this, we calculated the 95% CIs of the proportions (2, 3, 4) reported by the authors. Our results are presented in Table 1. When viewed in isolation, the FLC assay is clearly superior to serum immunofixation electrophoresis (IFE) for the detection of primary amyloidosis [88.3% (85.7%–90.9%) vs 73.8% (70.2%–77.4%)], but inferior as a stand-alone test for MGUS [42.2% (38.0%–46.4%) vs 92.8% (90.5%–95.15%)].

The statement by Katzmman et al. (1) that use of a simplified screening panel led to a reduction in sensitivity for detecting plasmacytoma does not appear to be substantiated by their data, because the 95% CIs of the 2 approaches clearly overlap [86.2% (73.0%–99.4%) for serum protein electro-

phoresis (PEL) plus FLC vs 89.7% (77.5%–100%) for all 5 tests].

Katzmann et al. reported that when they compared serum PEL and serum IFE with either FLC or urine IFE, the FLC assay appeared to offer a marginal increase in sensitivity over urine IFE in detecting multiple myeloma, but when the CIs are considered this apparent benefit disappears [100.0% (99.4%–100%) vs 98.7% (97.5%–99.9%)].

In the report by Katzmman et al., an additional column in Table 2 showing the results of serum PEL and serum IFE as a combination would allow for a more meaningful comparison with PEL and FLC as components of an alternative testing strategy. Without these results the information provided by Katzmman et al. does not make possible the accurate estimation of the yield of serum PEL and serum IFE as a stand-alone strategy. Therefore it is not possible to verify the statement by Katzmman et al. that “serum PEL and/or IFE should be used in combination with either urine IFE and/or serum FLC.”

Presenting the findings of complex comparisons with limited space can be challenging, but the use of appropriate statistical analysis and

relevant CIs aids in the interpretation of data and allows readers to judge the validity of conclusions reached (4, 5). In our opinion, the usefulness of the data in the report by Katzmman and coworkers will be enhanced by the addition of the information discussed above.

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In Reply

We agree with Pretorius and colleagues that CIs for screening panels for the detection of the various plasma cell proliferative disorders are a useful addition. Our decision to present the number and percentage of cases detected with various screening panels allows the reader to make these computations (1). There are many points raised by Pretorius and colleagues that need clarification. First, the serum free light chain (FLC)¹ assay is a simple serum test that can be readily performed even

on serum samples obtained for other purposes. On the other hand, urine electrophoresis and urine immunofixation studies require urine collection, making these tests more inconvenient and reducing physician ordering and patient compliance. When we evaluate the various strategies for diagnosing monoclonal gammopathies, although sensitivity is a major consideration, it is not the only consideration. In diagnostic categories in which urine immunofixation electrophoresis (IFE) and serum FLC contribute equally to diagnostic sensitivity (e.g., plasmacytoma), patient compliance needs to be considered. The submission of a urine sample for a screening test varies by the patient population studied, and inconvenience and low compliance are major problems. In hospitalized patients, the need for the urine sample may extend the hospital stay by an extra day. Therefore, even if urine IFE and serum FLC perform comparably in terms of sensitivity, the outcomes will be better for panels containing serum FLC if compliance is superior. Finances must also be considered. The costs of testing as well as reimbursement policies vary between laboratories. Thus, the serum FLC assay need not be superior to urine studies in terms of sensitivity, just not significantly inferior, to make it a useful and in most cases the preferred alternative.

Second, our goal in screening for possible plasma cell disorders is in most cases directed at ruling out malignancy (myeloma, macroglobulinemia, plasmacytoma) or light-chain amyloidosis. Except in certain specific instances (e.g., evaluation of a patient with unexplained neuropathy) we are not clinically interested in detecting asymptomatic monoclonal gammopathy of uncertain significance (MGUS). In fact, screening for MGUS is not proven to be effective and is not recommended. Thus if the proposed screening panel with serum FLC has lower sensitivity and

“misses” some patients with MGUS, it is not of clinical consequence, and may even be desirable. In contrast, what we are keen on is to maintain a high sensitivity for detecting malignancy or light-chain amyloidosis. Accordingly, it is true that only 10% of 5168 MGUS patients had all the assays performed, and only these 524 MGUS patients were included in the study. We recognize that selection bias is always a potential confounder of retrospective studies. However, as discussed earlier, we do not consider it a disadvantage that the combination of serum FLC plus electrophoresis is less sensitive for the diagnosis of MGUS, because that is not the diagnostic outcome of interest in most clinical situations.

Finally, the implied assertion that if the CIs overlap then the test panels are not different is not correct. Because multiple tests are performed on the same patients, any *P* value computation must take into account the pairing. When we use McNemar's test to compute *P* values for diagnostic sensitivity for panels containing serum protein electrophoresis, IFE, and FLC compared to serum protein electrophoresis and FLC there is a statistically significant decrease in sensitivity when screening for amyloidosis (*P* = 0.03), POEMS (polyneuropathy organomegaly endocrinopathy monoclonal gammopathy and skin changes syndrome) (*P* = 0.008), and MGUS (*P* < 0.001). The same analyses for panels with and without urine IFE show a statistically significant decrease in sensitivity for amyloidosis (*P* = 0.01). As suggested by Pretorius et al., plasmacytoma detection has no significant decrement in sensitivity when serum and urine IFE are omitted. We believe, however, that focusing on *P* values rather than the raw data is not the best approach. The use of serum FLC instead of urine IFE allowed

¹ Nonstandard abbreviations: FLC, free light chains; IFE, immunofixation electrophoresis; MGUS, monoclonal gammopathy of uncertain significance.