Reflex Testing of Free Prostate-Specific Antigen as Effective Health Care Policy

To the Editor.—We read with interest the article by Schifman et al[1] dealing with the utilization of measurement of free prostate-specific antigen (fPSA). We would like to contribute by reporting our experience about the management of fPSA requests by using a reflex testing approach and briefly discuss the status of the analytic control of this measurement.

Guidelines recommend testing fPSA to differentiate benign hyperplasia from prostate cancer only when total PSA (tPSA) concentrations in serum range between 4 and 10 μg/L (ng/mL) (revised after the assay recalibration, using the World Health Organization standards, to 3–10 μg/L [ng/mL]).[2] Studies have identified the optimal fPSA/tPSA cutoff as 20%, which effectively reduces the number of unnecessary biopsies.[3] In 2006, by auditing fPSA requests in our institution, we reported that only 16% (352 of 2247) of those requests complied with this recommendation, with an economic waste for our health care system of ~$56,250 USD per year.[4] These data supported the activation of an automatic reflex test allowing fPSA determination only when tPSA falls within the recommended concentration interval and labelling as "inappropriate" the fPSA requests in samples with tPSA out of the recommended limits. This reflex testing was first introduced for inpatients and 6 years later for outpatients, for whom the rate of inappropriate requests was even higher, with a tPSA ordering associated to fPSA in approximately 44% (2160 of 4871) of cases.

After 12 years, we recently audited our laboratory data showing that the fPSA reflex testing works very well in decreasing the test inappropriateness, 95.9% (1772 of 1848) being the rate of appropriately measured fPSA. Considering the last 6-month data, the distribution of detectable fPSA values (limit of detection, 0.01 μg/L [ng/mL]; Cobas e801, Roche Diagnostics, Mannheim, Germany) showed a median value (25–75th percentiles) of 0.70 (0.54–0.99) μg/L (ng/mL). Regarding the quality of measurements, we resorted to results from external quality assessment (EQA) to define (1) the actual state of harmonization of running fPSA assays at the concentrations mentioned above, and (2) whether the concentrations of distributed EQA samples fit with them. Data from the national Qualimedlab EQA (www.qualimedlab.it) (2016–2018 exercises) for the 4 most popular assays (Abbott Architect, Beckman Coulter Access/Dx, Roche Modular/Elecsys/Cobas, and Siemens Advia Centaur) on overall concentration means of fPSA <1 μg/L (ng/mL) showed a marked positive bias for Beckman Coulter systems (on average +25%), with other assays being characterized by a negative bias ranging from −1.4% to −10%.[5] According to these data and to the recently published specifications for fPSA bias (≤11.7%),[6] we can conclude that the harmonization of fPSA results obtained by the commercially available measuring systems is acceptable enough, with some exceptions. However, we should observe that in EQA schemes only fewer than 50% (8 of 18 per year) of exercises account for samples with fPSA concentrations below 1 μg/L (ng/mL), which mirror the distribution of fPSA concentrations in appropriate orders.

In conclusion, the use of reflex testing practice for fPSA should be strongly recommended as health care policy and implemented to pursue appropriate ordering and maximize clinical effectiveness. EQA providers should, however, pay more attention to fPSA concentrations of control materials to better evaluate the clinical suitability of available assays.

Simona Ferraro, BSc; Simone Caruso, MD; Mauro Panteghini, MD

Clinical Pathology Unit, ASST Fatebenefratelli-Sacco, Milan, Italy

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In Reply.—We appreciate learning about how the utilization of free prostate-specific antigen (PSA) is managed at your facility. It was interesting to read that only about 16% of free PSA orders met guidelines, which was comparable to the proportion of cases (163 of 790, 20.6%), collectively that met similar testing criteria, among 28 Q-Probes participants.[1] Use of a reflex testing protocol in which total PSA is evaluated first as a prerequisite step to determine if free PSA is performed was a sound practice, which effectively eliminated most of the waste from unnecessary testing. Another potential benefit derived from reflex free PSA testing worth noting is prevention of diagnostic error by reducing risk that free PSA may be clinically misapplied if reported when total PSA is outside the interpretable range.

Ron B. Schifman, MD[1]; Peter L. Perrotta, MD[2]; Barbara J. Blond, MBA, MT(ASCP)[3]

[1] Pathology and Laboratory Medicine, Southern Arizona VA Healthcare System, and the Department of Pathology, University of Arizona, Tucson; [2] Department of Pathology, University of West Virginia, and Clinical Laboratories, West Virginia University Hospital, Morgantown; [3] Surveys–Cytopathology, College of American Pathologists, Northfield, Illinois

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